Natural Product Synthesis

Studies Directed toward the Total Synthesis of Lactonamycin: Control of the Sense of Cycloaddition of a Quinone through Directed Intramolecular Catalysis**

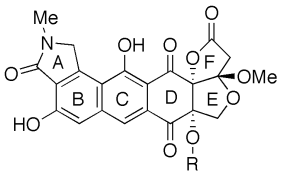
*Christopher D. Cox, Tony Siu, and Samuel J. Danishefsky**

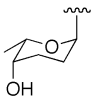
As part of a screening program for the discovery of new antibiotics, Matsumoto et al. isolated lactonamycin (**1**) from a culture broth of *Streptomyces rishirienisi* MJ773–88K4.[1] Its

[*] Prof. S. J. Danishefsky, Dr. C. D. Cox, T. Siu
Department of Chemistry, Columbia University
Havemeyer Hall, New York, NY 10021 (USA)
E-mail: s-danishefsky@ski.mskcc.org
Prof. S. J. Danishefsky
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Ave., New York, N.Y. 10021 (USA)
Fax: (+1) 212-772-8691

[**] This work was supported by the National Institutes of Health (Grant number: HL25848). A Postdoctoral Fellowship is gratefully acknowledged by C.D.C. (NIH, Grant Number F32-CA84758). The authors thank Yashuiro Itagaki for high-resolution mass spectral analyses.

 DOI: 10.1002/ange.200352591 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



1 R = 

2 R = H

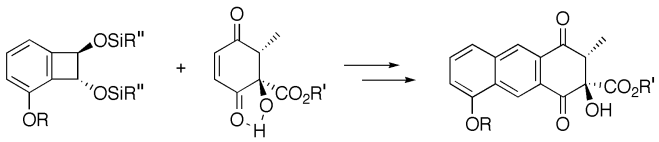
structure and absolute configuration were assigned through spectroscopic and X-ray crystallographic measurements in conjunction with degradation protocols. Biological evaluation of lactonamycin revealed it to have antimicrobial activity against Gram-positive bacteria, including methicillin- and vancomycin-resistant strains ($IC_{50} = 0.20$–$1.56\ mg\,mL^{-1}$). In addition to its antimicrobial activities, lactonamycin is cytotoxic against various tumor cell lines ($IC_{50} = 0.06$–$3.3\ mg\,mL^{-1}$).

The novel, highly functionalized hexacyclic aglycone domain of lactonamycin, lactonamycinone (**2**), inherently poses some significant issues at the planning level of a chemical synthesis. Furthermore, the feasibility of glycosylation of a tertiary α-hydroxyketone acceptor site with an appropriate L-rhodinose donor species under high anomeric stereoselectivity could hardly be taken for granted. These concerns notwithstanding, the challenges confronting any attempt to construct lactonamycin in a laboratory setting and its promising profile of antibiotic action drew us into a total synthesis venture. We report herein an important milestone in that effort, that is, the first total synthesis of the aglycone, lactonamycinone (**2**).[2] We expand upon the concept of intramolecular directed catalysis, which enabled the highly concise assembly of the key tetracyclic intermediate **35** (see Scheme 7), and we discuss how we overcame the many difficulties associated with the synthesis of this intermediate and its conversion into lactonamycinone.[3]

Our strategy hinged on the condensation of a homophthalic anhydride (see generalized structure **3**) with a quinone **4** in a process that is initiated by an anionically mediated "cycloaddition" reaction (Scheme 1). We use the term cycloaddition in an empirical rather than mechanistic sense, thereby sidestepping difficultly resolvable issues related to the concerted nature of the reaction. Cycloadduct **5** would be expected to undergo transformation into **6** upon the loss of carbon dioxide. Although this type of overall reaction is, in itself, well-known as a Tamura–Diels–Alder reaction,[4] in this case it was to be applied to the unsymmetrical quinone **4**. Even if unlikely initial cycloaddition at the more hindered of the quinone double bonds is neglected, in principle, two regioisomeric products **6** and **8**, arising from primary cycloadducts **5** and **7**, respectively, could be produced.

In Scheme 1, a general format for solving this type of problem is suggested by building an internal activating group into the quinone **4**. In the case at hand, we imply that the formal ketone group (a) can be rendered more active than its counterpart (b) by means of the biasing element X.[5a–c] Whether through hydrogen bonding or metal-ion bridging (see below), the consequences of this intramolecular directed catalysis would be to favor the eventual formation of **6** over **8**.

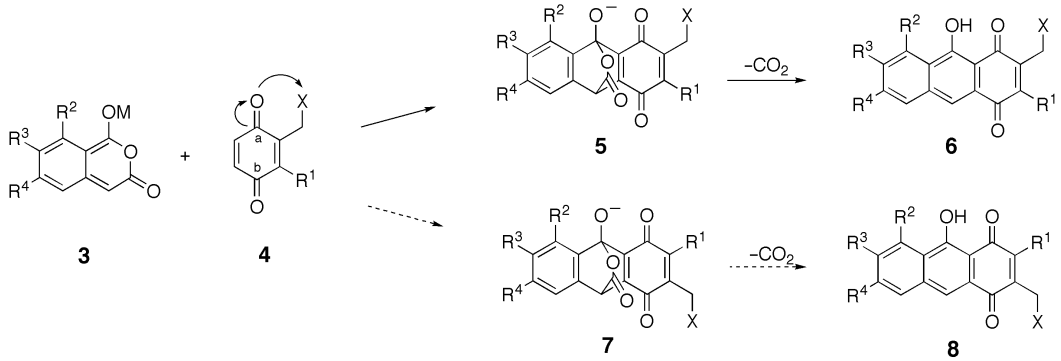
Indeed, in our recently described total synthesis of rishirilide B, we demonstrated this type of locally biased catalysis (Scheme 2, **9** + **10**→**11**).[6] In the total synthesis of



9 **10** **11**

Scheme 2. Application of locally biased catalysis in the total synthesis of rishirilide B.

lactonamycin, we hoped to extend the local biasing strategy to quinones rather than to a cyclohexene-1,4-dione **10**. Since quinones are particularly reactive substrates, the applicability of the findings in the case of rishirilide was open to question. Moreover, we would be seeking to extend the generalized idea of regiocontrol by intramolecular catalysis from a clear cycloaddition case (**9** + **10**) conducted under neutral conditions to a less-well-defined, anion-mediated setting (**3** + **4**).

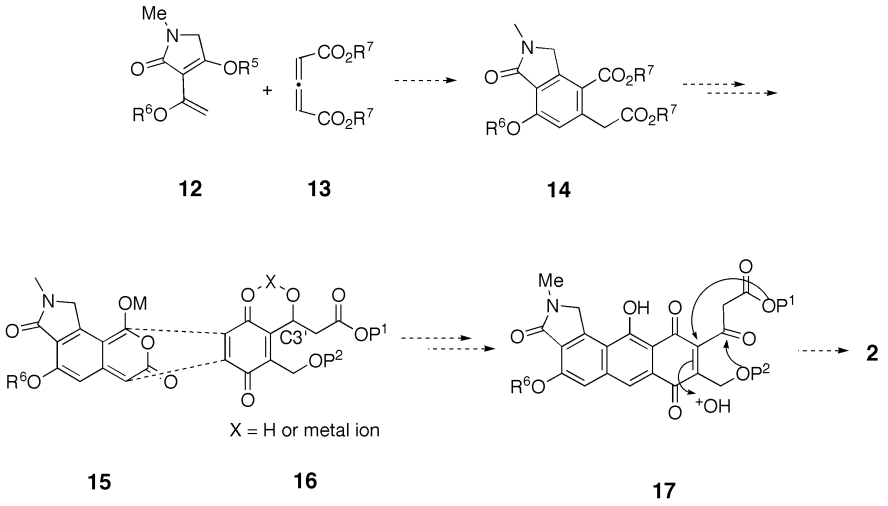


3 **4** **5** **6** **7** **8**

Scheme 1. Tamura–Diels–Alder reaction with an unsymmetrical quinone.

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

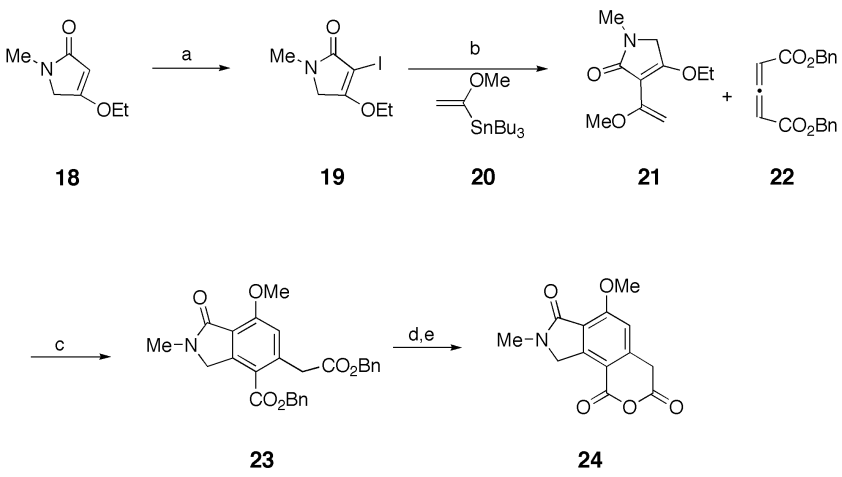
Viewed from the perspective of lactonamycinone, we envisioned the cycloaddition of **15** and **16** (Scheme 3). The orienting function would be the strategically placed hydroxy group at C3′, which would differentiate the two ketone-like centers of quinone **16**. We hoped to reach the homophthalic anhydride **15** by a Diels–Alder reaction of **12** and **13**. In this way, we would ultimately have connected the diverse functionalities of the ABCD ensemble through *two* defining cycloaddition reactions (see product **17**). Some of the necessary connections to proceed from **17** to lactonamycinone (**2**) are suggested in Scheme 3.



12 **13** **14** **15** **16** **17**

Scheme 3. Proposed synthesis of lactonamycinone

Implementation of the ideas outlined above commenced with tetramic acid derivative **18**[7] (Scheme 4). Iodination[8] of this compound gave rise to **19**, which served as a substrate for a Stille reaction with **20**,[9] thereby giving rise to diene **21** in 42% yield (two steps). For our allene component, we took recourse to the 1,3-dicarbobenzyloxyallene (**22**).[10] In the event, cycloaddition of **21** and **22** was possible and gave **23**, albeit in 15–25% yield. Hydrogenolysis of the two benzyl esters gave rise to a diacid. However, dehydration with trimethylsilylethoxyacetylene[11] only produced trace amounts of the desired homophthalic anhydride **24**, presumably as a result of solubility issues. It is possible that the difficulties in the cycloaddition reaction of **21** and **22** reflect the usual complexities associated with Diels–Alder reactions of 1,1-disubstituted dienes, in which the required 2,3-*s-cis* coplanar conformer may be of high energy. In the case at hand, the situation is perhaps further aggravated by the presence of substituents at C2 and C3 in **21**. Given the difficulties of the Diels–Alder reaction and anhydride formation, we also explored an alternative route, which, though somewhat less concise, lends itself to larger-scale development.



18 **19** **20** **21** **22** **23** **24**

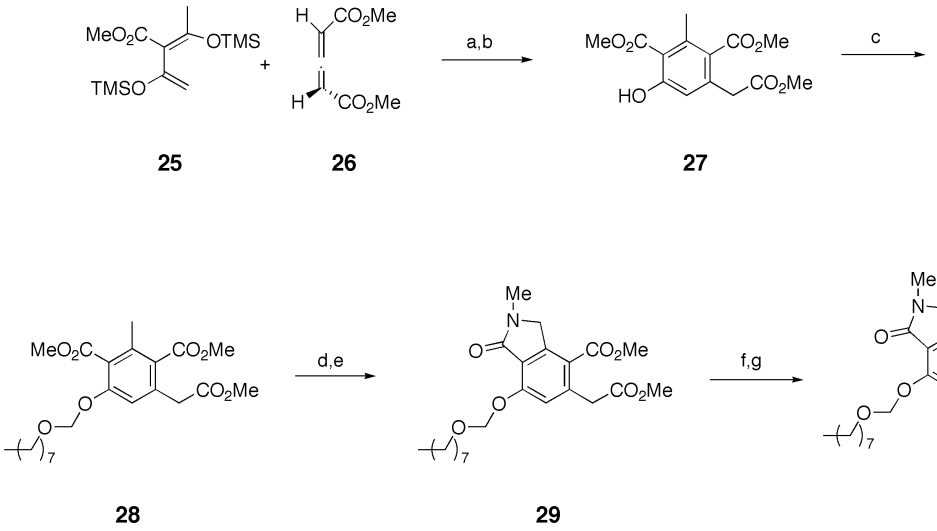
Scheme 4. Reagents and conditions. a) I_2, PIFA, pyridine, 51%; b) **20**, $[PdCl_2(PPh_3)_2]$, PhMe, reflux, 83%; c) **22**, neat, 200°C, 15–25%; d) H_2, Pd/C, 50%; e) trimethylsilylethoxyacetylene, CH_3CN/CH_2Cl_2, trace amounts of product. PIFA = bis(trifluoroacetoxy)iodobenzene.

The second path started with the known bis(silyl enol ether) **25**.[12] Cycloaddition of **25** with the 1,3-dicarbomethoxyallene (**26**)[10] gave rise to **27** in 75% yield (Scheme 5). To overcome issues of solubility later in the synthesis, the phenolic function of **27** was protected as an unconventional octyloxymethyl ether[13] derivative **28**. The aryl methyl group of **28** was brominated with *N*-bromosuccinimide and benzoyl peroxide under irradiation from a UV lamp. Revisiting a type of chemistry that we had studied in 1969, we treated the resulting compound with methylamine, which gave rise primarily to lactam **29**[14] (30% yield based on recovered starting material) along with the isomeric isoindolinone (3.5:1). Hydrolysis of the ester linkages gave rise to a diacid, which was dehydrated to produce the protected pyrrolo homophthalic anhydride **30** (Scheme 5).

The building of a suitable quinone system started with the known **31**[15] (Scheme 6). Protection of the primary alcohol as a benzyl ether followed by deprotection of the dithiane[16] afforded **32** in 74% yield. The smooth chain extension of the benzaldehyde derivative by the Rathke methodology[17] gave rise to **33** in excellent yield. Oxidative demethylation of this substrate afforded quinone **34** in 96% yield. It was this compound that would serve as the coupling partner with the previously described homophthalic anhydride **30**.

With the appropriately functionalized quinone **34** and homophthalic anhydride **30** in hand, the crucial Tamura–Diels–Alder reaction was examined. In the event, treatment of **30** with 2 equivalents of NaH at −78°C, followed by the addition of 2 equivalents of quinone **34** and warming to 0°C, led to a rapid cycloaddition reaction followed by extrusion of

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



25 **26** **27**

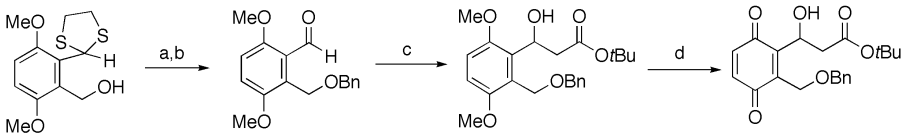
28 **29** **30**

Scheme 5. Reagents and conditions. a) **25, 26**, neat, 105 °C; b) NH_4F, MeOH, 75 %; c) $CH_3(CH_2)_7OCH_2Cl$, DIPEA, DMF, 95 %; d) NBS, benzoyl peroxide (cat.), UV, benzene; e) K_2CO_3, NH_2Me, MeOH/CH_3CN (1:2), 30 % yield based on recovered starting material, 3.5:1; f) KOH, MeOH, 98 %; g) trimethysilylethoxyacetylene, CH_3CN/CH_2Cl_2, quantitative. DIPEA = *N,N*-diisopropylethylamine; DMF = *N,N*-dimethylformamide.

carbon dioxide to provide quinone **35** in 40 % yield (Scheme 7). As we had hoped, only a single regioisomer was formed, as determined by NMR spectroscopic analysis at 500 MHz. The structure of the product was first inferred from precedent and later confirmed by X-ray crystallography to correspond to that depicted in **35**. Notably, 2 equivalents of quinone were needed for optimum yield—presumably the extra equivalent is required to oxidize the resulting hexacyclic intermediate to quinone **35**. Efforts to use 1 equivalent of quinone and an external source of oxidant gave lower yields.

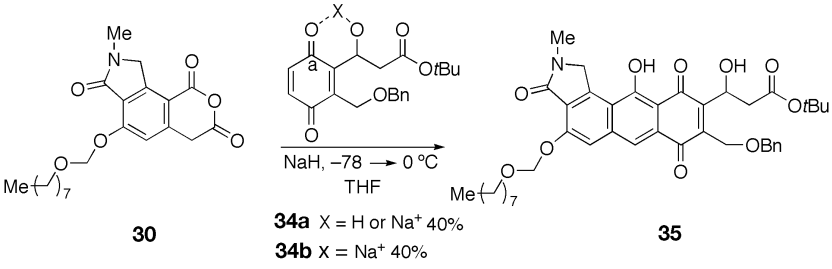
Although we had indeed predicted the preferred formation of **35** under mediation by a strategically placed activating group, it was appropriate to test this rationale in a closely related setting, thereby enabling further understanding of the issues involved. Accordingly, the hydroxy group of **34** was protected as its *tert*-butyldimethylsilyl ether **36**. The latter compound reacted smoothly under the same Tamura–Diels–Alder reaction conditions employed for **35** (Scheme 8). However, in this case a 1:1 mixture of **37** and **38** was produced. Certainly, this experiment is fully in keeping with the governing paradigm sketched out in Scheme 1 (see structure **4**).

In presenting this model for directed activation we were appropriately vague as to the precise nature of the activating



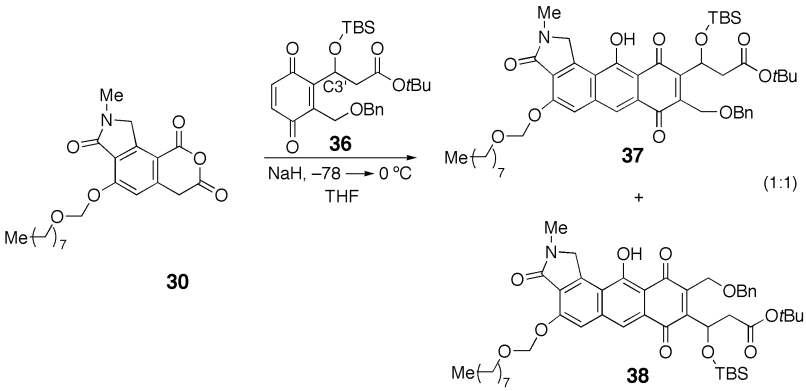
31 **32** **33** **34**

Scheme 6. Reagents and conditions. a) NaH, BnBr, TBAI, THF, 86 %; b) PIFA, CH_3CN/H_2O (1:1), 86 %; c) LDA, *t*BuOAc, −78 °C, THF, 99 %; d) CAN, 0 °C, CH_3CN/H_2O (9:1), 96 %. TBAI = tetrabutylammonium iodide; LDA = lithium diisopropylamide; CAN = ceric ammonium nitrate.



30 **34a** X = H or Na^+ 40 % **34b** X = Na^+ 40 % **35**

Scheme 7. Regioselective Tamura–Diels–Alder reaction.



30 **36** **37** (1:1) **38**

Scheme 8. Disruption of the locally biased catalysis.

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

effect. One possibility would be that of a local intramolecular hydrogen bond. Alternatively, carbonyl a (**34a**) could be differentially activated by a chelation effect (sodium in the case of our application of the Tamura reaction). Clearly, a metal chelate effect might, in principle, have been possible even if the oxygen atom of the side chain were protected as the TBS ether. Since TBS ethers projecting from carbons α or β to a carbonyl function tend to be poor donors to support metal-mediated chelates,[18] the 1:1 ratio of products resulting from the reaction of **30** and **36** is not surprising.

Finally, we probed the possibility of exerting control through an alkoxide-based metal bridge. Toward this end, compound **34** was pretreated with NaH. Treatment of **34b**, thus produced, with **30** under the same conditions used above again led to **35** as the only isolated regioisomer (Scheme 7). Hence, metal-induced positionally directed selective activation is clearly possible with a hydroxy-based anchor (see **34b**). It remains to be shown whether a hydrogen-bonded counterpart can intervene under these basic conditions.

In summary, we have shown how the otherwise complicated ABCD domain of lactonamycin can be assembled with high regiocontrol through two cycloaddition reactions from readily synthesized components. This enabling strategy was crafted around the notion of gaining regiochemical control through mediation of a suitably positioned hydroxy group. The concept was reduced to practice but does not extend to the corresponding TBS ether of the hydroxy group. In the following Communication in this issue, we describe the completion of the total synthesis of lactonamycinone utilizing the key ideas and intermediates illustrated herein.

Received: August 7, 2003 [Z52591]

Keywords: antibiotics · Diels–Alder reaction · natural products · quinones · total synthesis

[1] a) N. Matsumoto, T. Tsuchida, M. Maruyama, R. Sawa, N. Kinoshita, Y. Homma, Y. Takahashi, H. Iinuma, H. Naganawa, *J. Antibiot.* **1996**, *49*, 953 – 954; b) N. Matsumoto, T. Tsuchida, M. Maruyama, N. Kinoshita, Y. Homma, H. Iinuma, T. Sawa, M.; T. Hamada, T. Takeuchi, N. Heida, T. Yoshioka, *J. Antibiot.* **1999**, *52*, 269 – 275; c) N. Matsumoto, T. Tsuchida, H. Nakamura, R. Sawa, Y. Takahashi, H. Naganawa, H. Iinuma, T. Sawa, T. Takeuchi, M. Shiro, *J. Antibiot.* **1999**, *52*, 276 – 280.

[2] For synthetic and model studies toward the synthesis of lactonamycin, see: a) C. Cox, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 3493 – 3496; b) C. Cox, S. J. Danishefsky, *Org. Lett.* **2001**, *3*, 2899 – 2902; c) J. P. Deville, V. Behar, *Org. Lett.* **2002**, *4*, 1403 – 1405d) T. R. Kelly, D. Xu, G. Martinez, H. Wang, *Org. Lett.* **2002**, *4*, 1527 – 1529.

[3] T. Siu, C. D. Cox, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 5787 – 5792; *Angew. Chem. Int. Ed.* **2003**, *42*, 5629 – 5634.

[4] Y. Tamura, F. Fukata, M. Sasho, T. Tsugoshi, Y. Kita, *J. Org. Chem.* **1985**, *50*, 2273 – 2277, and references therein.

[5] For a related use of this concept in a Diels–Alder reaction, see: a) H. Fujioka, H. Yamamoto, H. Annoura, H. Maeda, Y. Kita, *Chem. Pharm. Bull.* **1992**, *40*, 32 – 35; for a related use of this concept in juglone and naphthazarin systems, see: b) V. H. Powell, A. J. Birch, *Tetrahedron Lett.* **1970**, *11*, 3467 – 3469; c) T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr. J. M. Lyding, *J. Am. Chem. Soc.* **1977**, *99*, 5513 – 5514.

[6] J. G. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 351 – 352.

[7] H. W. Pinnick, K. S. Kochhar, *J. Org. Chem.* **1989**, *54*, 3222 – 3224.

[8] R. Benhida, P. Blanchard, T. L. Fourrey, *Tetrahedron Lett.* **1998**, *39*, 6849 – 6852.

[9] J. A. Soderquist, J.-H. Hsu, *Organometallics* **1982**, *1*, 830 – 833.

[10] M. Node, T. Fujiwara, S. Ichihashi, K. Nishide, *Tetrahedron* **1986**, *42*, 6645 – 6656.

[11] P. Müller, N. Pautex, *Helv. Chim. Acta* **1991**, *74*, 55 – 64.

[12] P. Allevi, M. Anastasia, S. Bingham, P. Ciuffreda, A. Fiecchi, G. Cighetti, A. Scala, J. Tyman, *J. Chem. Soc. Perkin Trans. 1* **1998**, 575 – 582.

[13] A. Warshawsky, A. Deshe, *J. Polym. Sci. Part. A* **1985**, *23*, 1839.

[14] S. J. Danishefsky, T. A. Bryson, J. Puthenpurayil, *J. Org. Chem.* **1975**, *40*, 1846 – 1848.

[15] G. A. Kraus, L. Chen, R. A. Jacobson, *Synth. Commun.* **1993**, *23*, 2041 – 2049.

[16] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287 – 290.

[17] M. J. Rathke, D. F. Sullivan, *J. Am. Chem. Soc.* **1973**, *95*, 3050 – 3051.

[18] G. E. Keck, S. Castellino, *Tetrahedron Lett.* **1987**, *28*, 281 – 284.

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim