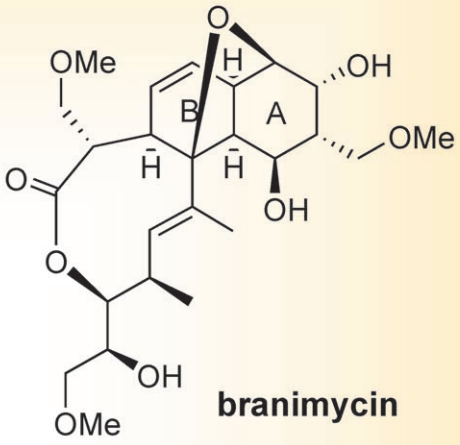
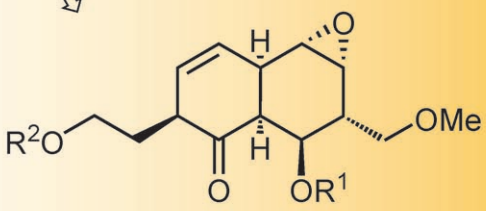
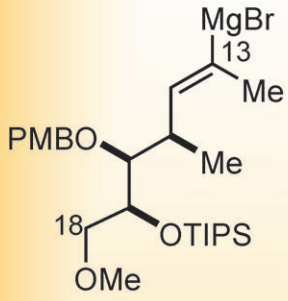
Towards the Synthesis of Antibiotic Branimycin



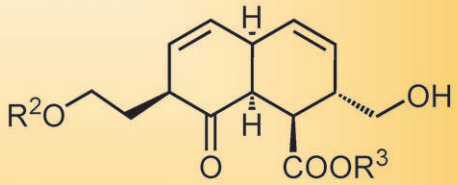
branimycin



octalin core



side chain



dehydrooctalin

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Toward the Synthesis of the Antibiotic Branimycin: Novel Approaches to Highly Substituted *cis*-Decalin Systems

Johann Mulzer,* Daniele Castagnolo, Wolfgang Felzmann, Stefan Marchart, Christian Pilger, and Valentin S. Enev*[a]

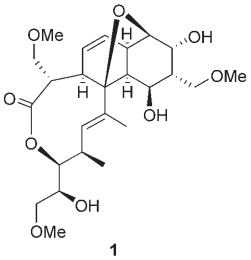
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

Abstract: A variety of highly functionalized *cis*-decalin systems have been prepared by means of the stereoselective transannular Diels–Alder (TADA) reaction of a (*Z*,*E*,*Z*,*Z*)-tetraene macrolide, and by means of intramolecular nitrile oxide olefin (INOC) or ring-closing metathesis (RCM) annulations to quinic acid derivatives.

Keywords: annulation · Diels–Alder reaction · ring-closing metathesis · stereoselective synthesis · synthesis design

Introduction

The increasing resistance of bacterial pathogens against standard antibiotics combined with an emerging threat of bioterrorism has led to the urgent need for developing innovative anti-infective drugs.[1] Recently, branimycin (**1**) has been isolated by the Laatsch group from *actinomyces* GW 60/1571[2].



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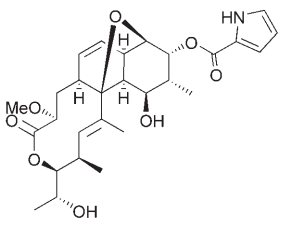

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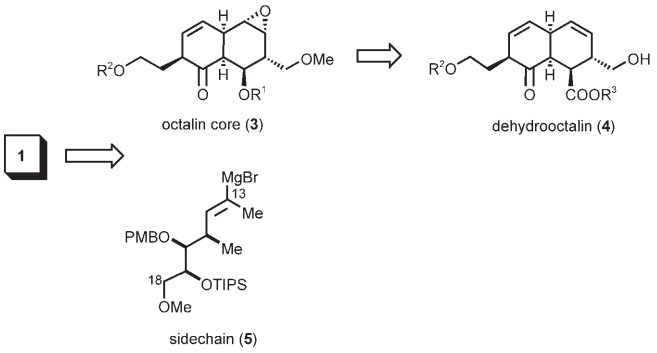
First biological tests have shown that **1** is highly active against *Streptomyces viridochromogenes*. The structure of **1** is related to that of the nargenicins[3] (e.g., nargenicin A1, **2**) and has been reliably elucidated by multidimensional ^{1}H and ^{13}C NMR experiments. The interesting biological activity and the complex molecular architecture make **1** an attractive target for total synthesis. Our retrosynthetic analysis (Scheme 1) features a disconnection of the molecule into a

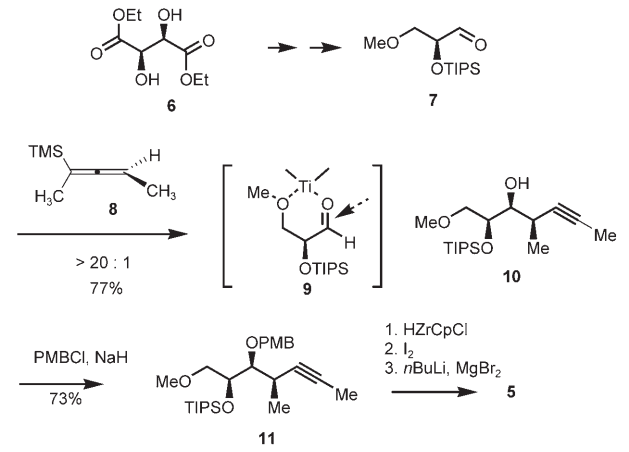


Scheme 1.

bicyclic *cis*-decalin type core (e.g., **3** or **4**) and a vinyl magnesium side chain (**5**). In this report we describe the synthesis of **5** and novel approaches to *cis*-fused decalin derivatives.

Synthesis of Side Chain 5

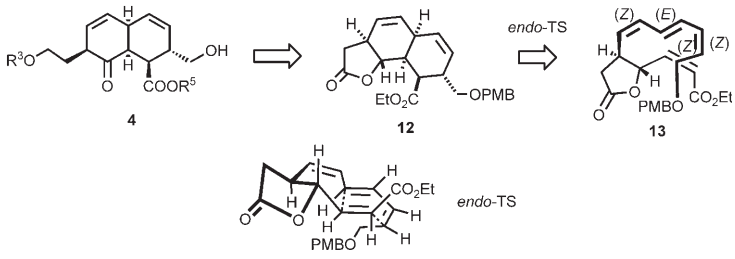
The synthesis started from natural (*R*,*R*)-diethyl tartrate (**6**), which was converted into the protected glyceraldehyde **7** (Scheme 2). Titanium tetrachloride mediated addition of the nonracemic allenylsilane **8**[4] resulted in the selective formation (d.r. >20:1) of the all-*syn* diastereomer **10**, presumably via a chelate intermediate **9**. Benzyl-protection led to **11** which was converted into **5** via a regio- and stereocontrolled hydrozirconation-iodination-metalation sequence.



Scheme 2.

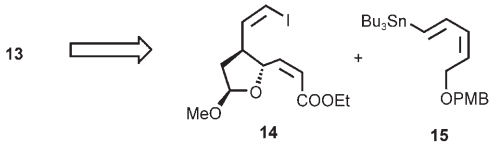
Synthesis of *cis*-Dehydrooctalin Lactone 12: The Transannular Diels–Alder (TADA) Approach

Following the retrosynthetic suggestion in Scheme 3, we aimed for a synthesis of **4** that should be prepared by means



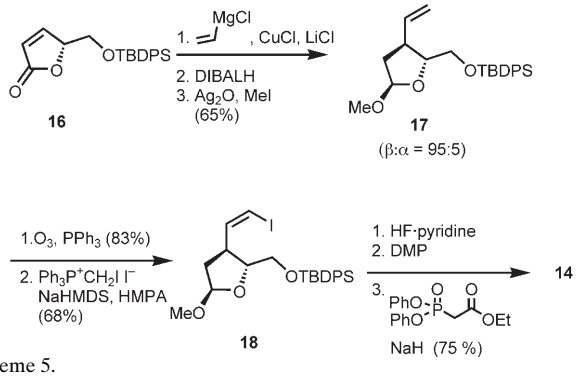
Scheme 3.

of a intramolecular Diels–Alder (IMDA) reaction[5] of tetraene **13**. In this manner, lactone **12** should be formed through an *endo*-transition state. Tetraene **13**, in turn, was to be constructed by a Stille coupling[6] of vinyl iodide **14** and vinyl stannane **15** (Scheme 4).



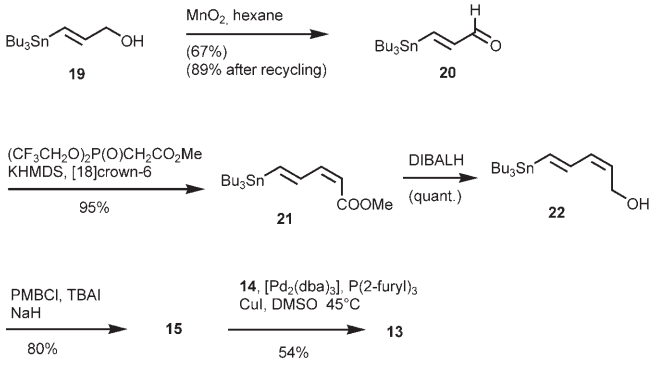
Scheme 4.

For the synthesis of **14**, lactone **16** was subjected to a stereoselective 1,4-addition of vinyl cuprate. As the lactone function turned out to be incompatible with the transformations envisaged later, it was reduced to the lactol and converted into acetal **17** with high stereocontrol. Oxidation of the olefinic sidechain to the aldehyde followed by a *cis*-selective Wittig olefination gave vinyl iodide **18** in good overall yield, which was transformed into (*Z*)-enoate **14** by means of an Ando olefination[7] (Scheme 5). The synthesis



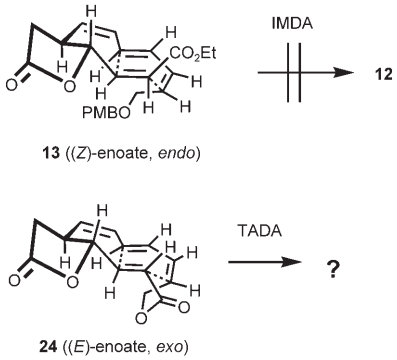
Scheme 5.

of dienyl-stannane **15** is outlined in Scheme 6. Allylic alcohol **19** was oxidized to aldehyde **20**, which was subjected to a Still–Gennari olefination to give ester **21** with high *Z* selectivity. Reduction with diisobutyl aluminium hydride and formation of the *p*-methoxybenzyl ether led to **15**. Stille coupling with **14** furnished geometrically pure tetraene **13** in satisfactory yield. The attempted IMDA reaction[5] failed under all conditions we tried (heating to 150 °C, addition of Lewis acids, high pressure up to 13 kbar). Instead, extensive *E*/*Z* isomerization was observed in the triene part of the molecule.

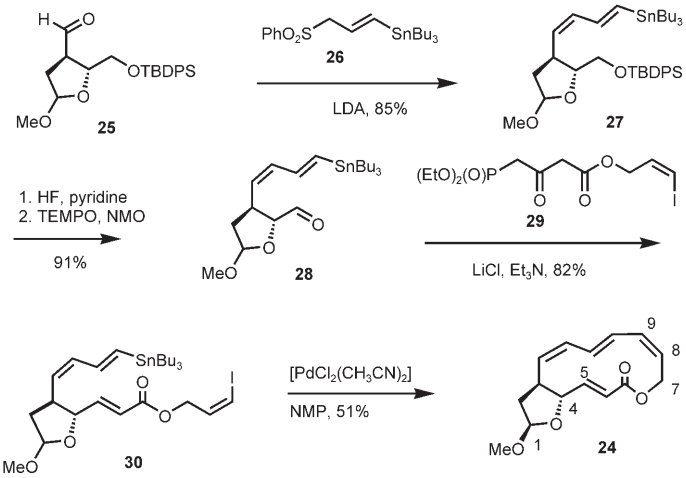


Scheme 6.

To remedy this situation, we decided to inhibit such isomerizations by incorporating the triene into a macrolide ring, such as **24**, and switch from IMDA to TADA[8] cyclization (Scheme 7). To achieve smooth macrocyclization, an (*E*)-enoate had to replace the former (*Z*)-enoate, and the former *endo* transition state had to be converted into the *exo* transition state. The synthesis of **24** (Scheme 8) was started with a (*Z*)-selective Julia olefination[9] of aldehyde **25** with sulfone **26** to give (*Z*,*E*)-diene **27**, which was oxidized to aldehyde **28** and olefinated to ester **30**. Stille macrocyclization[6] gave **24** in moderate yield.

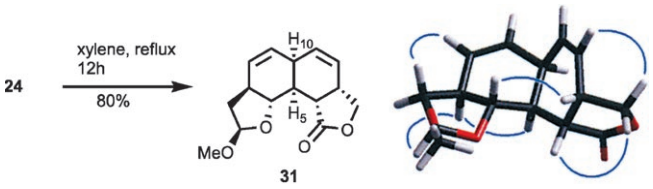


Scheme 7.



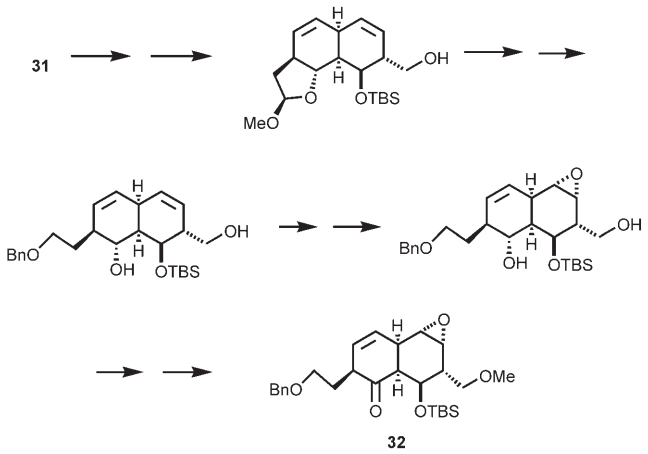
Scheme 8.

As expected, **24** underwent smooth TADA cyclization under thermal conditions (Scheme 9) to give the diastereomerically pure *cis*-dehydrooctalin lactone **31** according to



Scheme 9.

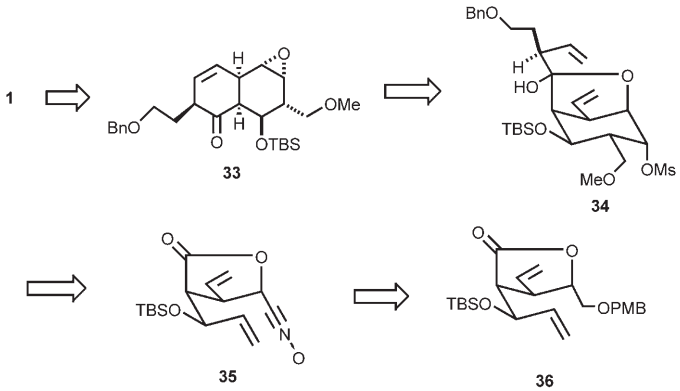
HPLC and NMR analysis. The relative configuration of **31** was elucidated by ^{1}NMR spectroscopy. Specifically, the low value of $J_{5,10}$ (6 Hz) and the NOE interactions shown in the three-dimensional representation strongly supported the configurations assigned. Further experiments are under way to convert **31** into octalin **32**, ready for connection with side chain **5** (Scheme 10).



Scheme 10.

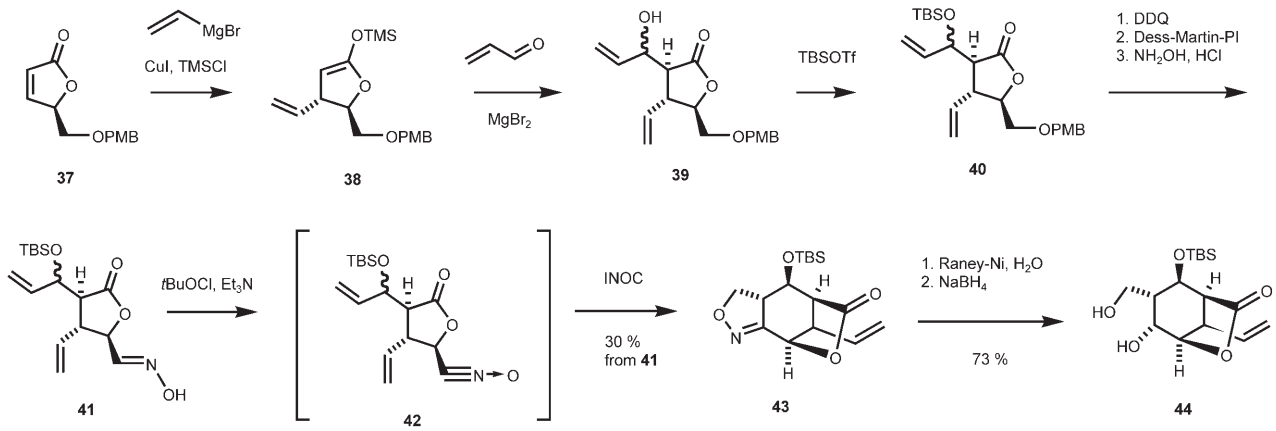
Intramolecular Nitrile Oxide Olefin (INOC) Cyclizations

In a second approach, the intramolecular nitrile oxide olefin (INOC) cyclization[10] was attempted for generating highly substituted cyclohexane and *cis*-decalin systems. Thus compound **33** was envisaged as a suitable core moiety of **1** (Scheme 11).



Scheme 11.

cis-Decalin **33** was to be derived from a ring-closing metathesis reaction[11] of diolefin **34**, which could be prepared from lactone **36** via nitrile oxide **35**. To probe the viability of this approach, lactone **37** was converted into **39** through the conjugate addition of vinyl cuprate and acrolein (Scheme 12). Unfortunately, **39** was obtained as an epimeric mixture and all attempts to generate **39** in epimerically pure form failed. Straightforward functional manipulation of this mixture furnished oxime **41**, which was oxidized to nitrile oxide **42**. Under the conditions in situ cyclization to diastereomerically pure isoxazoline **43** occurred, the configuration



Scheme 12.

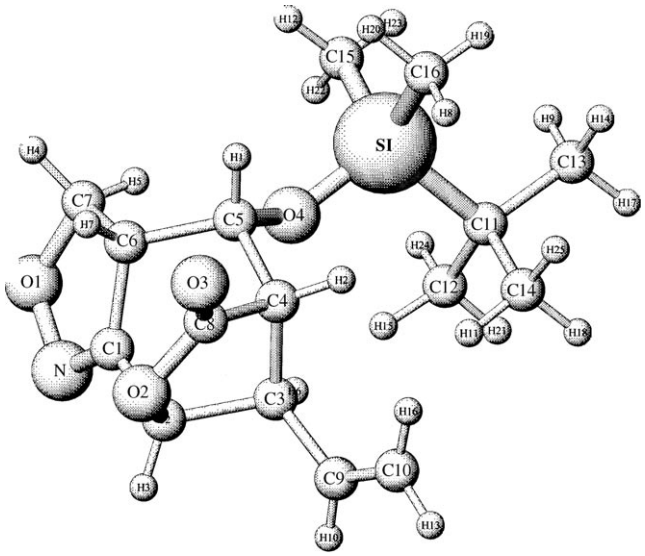
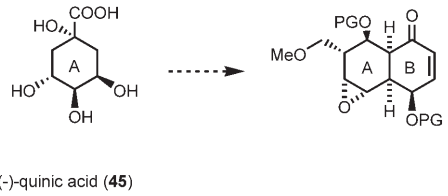
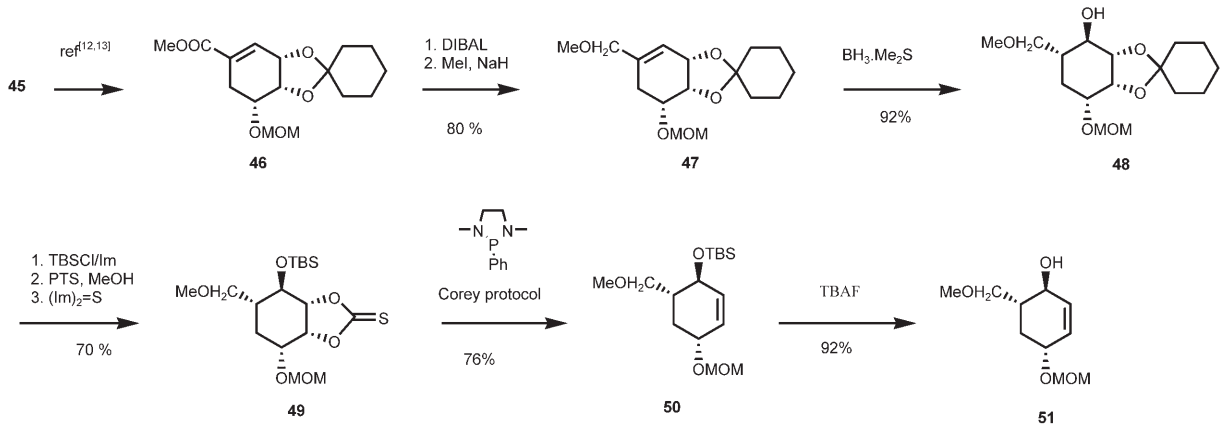


Figure 1. Crystal structure of compound **43**.



Scheme 13.

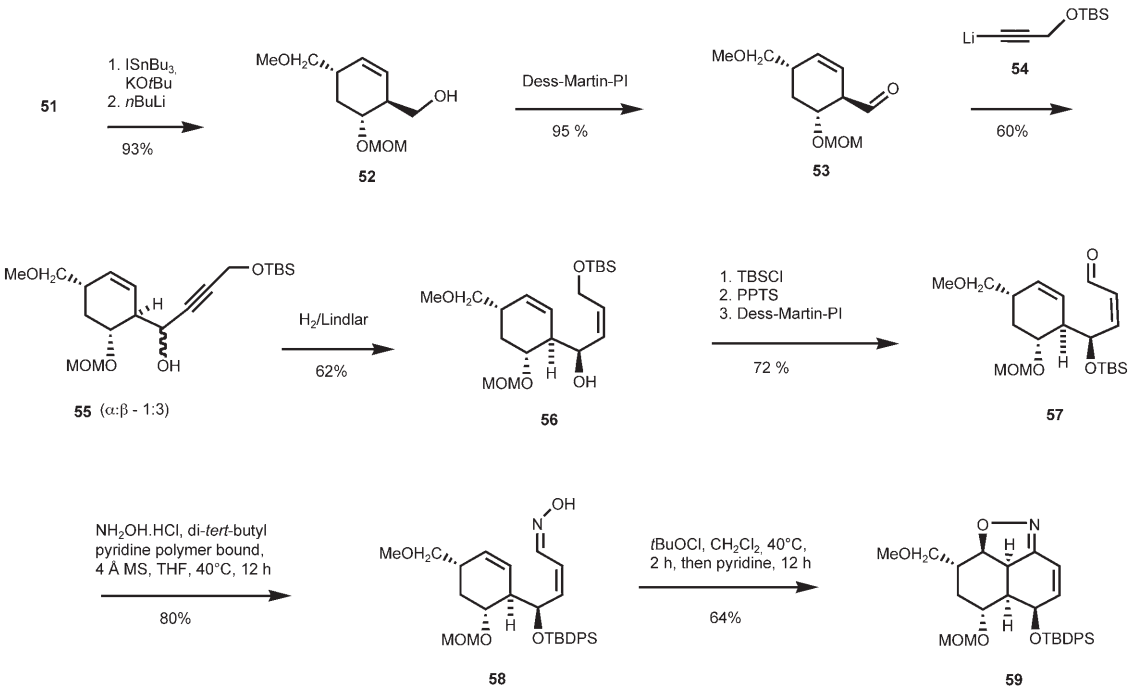
of which was elucidated by single-crystal diffraction (Figure 1). Only the β-OTBS diastereomer underwent the INOC reaction, the α-diastereomer did not give defined products. Although **43** could be converted into diol **44** with high stereocontrol, this approach was abandoned due to the low efficiency of the INOC step. Instead, it was decided to use the INOC reaction for an annulation of ring B to an already existing cyclohexene ring A, which should be derived from D-(−)-quinic acid (**45**) as an inexpensive chiral starting material (Scheme 13).



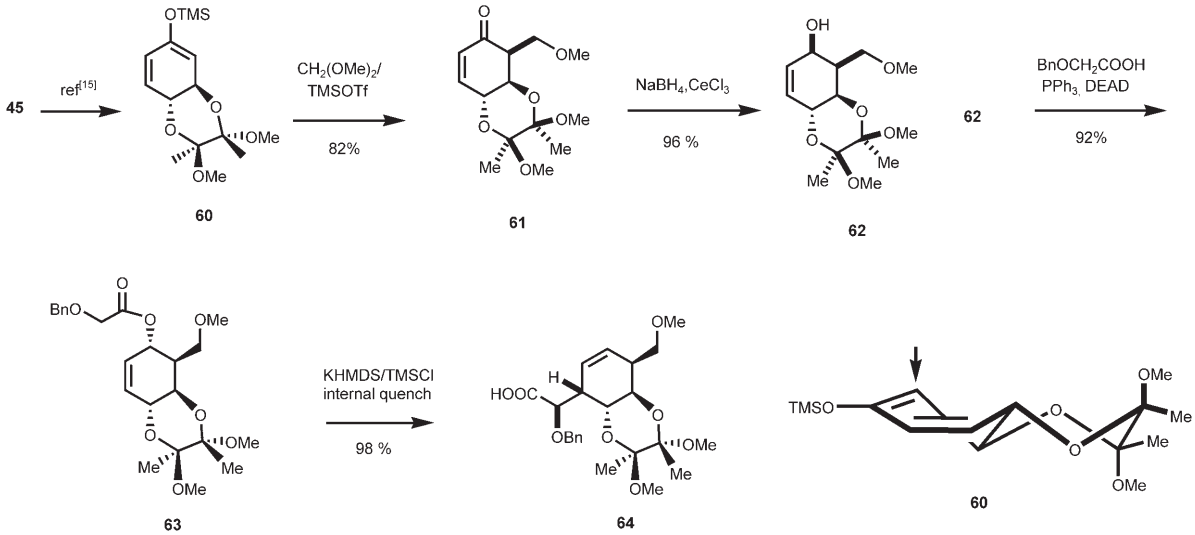
Scheme 14.

Hence, in a model study, **46** was prepared from **45** as described[12,13] and transformed into cyclohexene diol **51** by means of the sequence shown in Scheme 14, with stereocontrolled hydroboration/oxidation (**47** to **48**) and Corey–Hopkins elimination[14] (**49** to **50**) as the key steps.

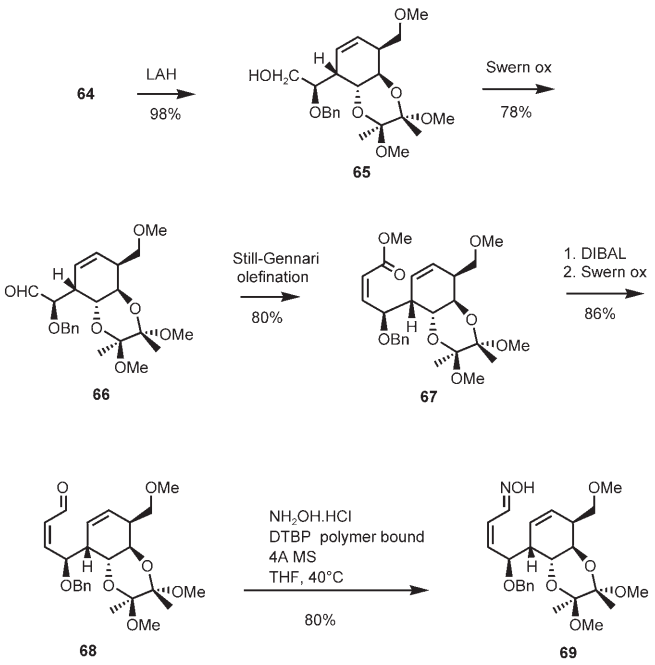
A Wittig–Still rearrangement was used to generate alcohol **52** (Scheme 15), which was oxidized to aldehyde **53**. Nonstereocontrolled addition of alkyne **54** furnished an epimeric mixture of alcohol **55** that was separated. The β-epimer was used in an INOC annulation via aldehyde **57** and oxime **58**, which were both stable towards *E*/*Z* isomerization. Nitrile oxide formation and cycloaddition occurred in situ to furnish isoxazoline **59** in a diastereomerically pure form. Encouraged by this success, we decided to prepare the fully substituted core compound. Thus, as shown in Scheme 16, **45** was converted into silyl dienol ether **60**,[15] to which dimethoxymethane was added under trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis with high axial prefer-



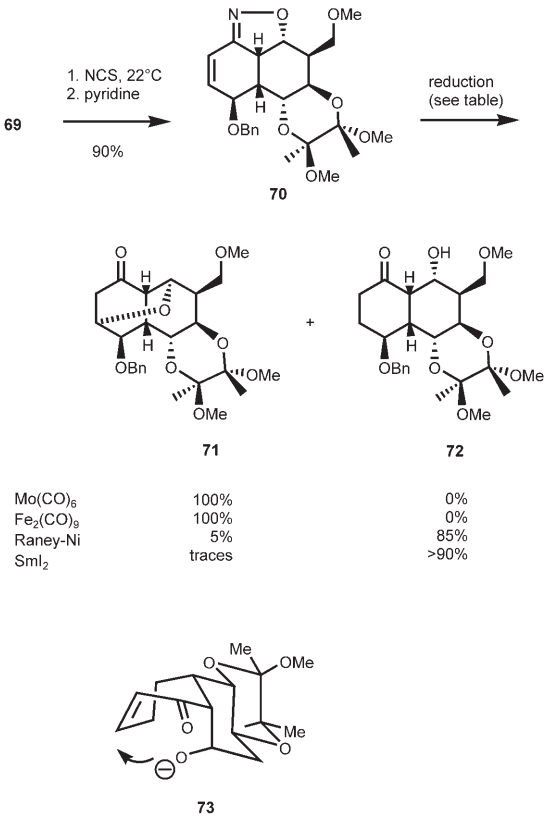
Scheme 15.



Scheme 16.

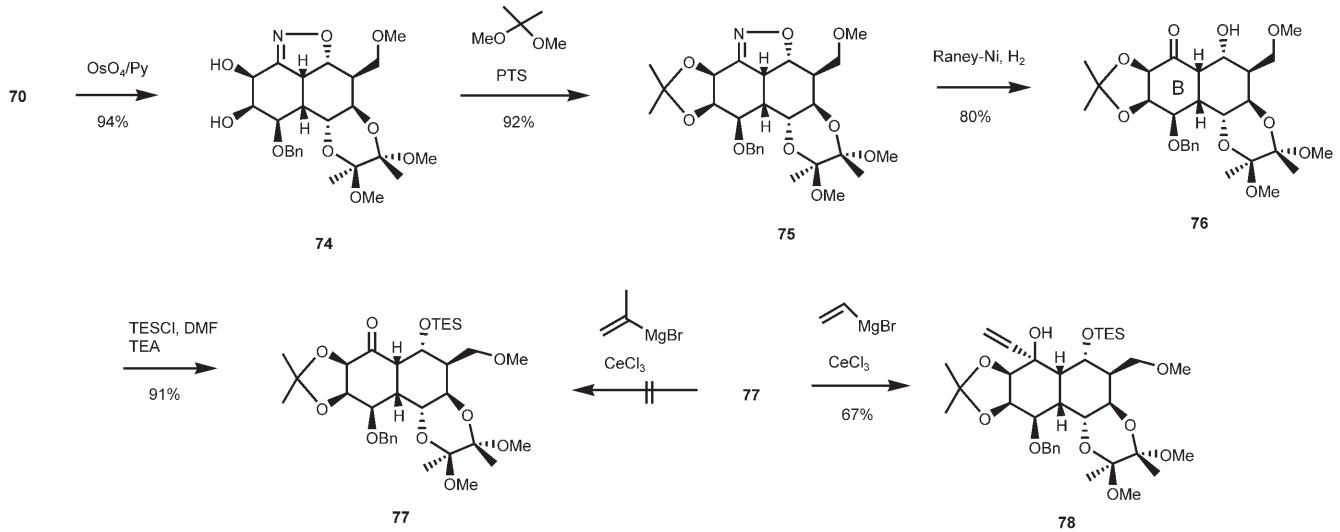


Scheme 17.

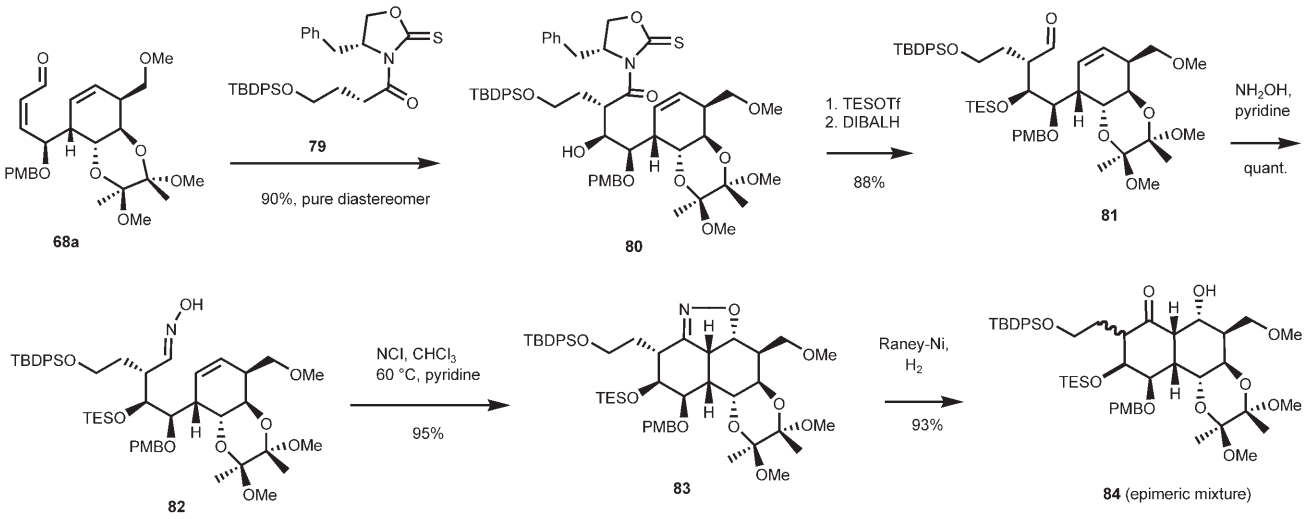


Scheme 18.

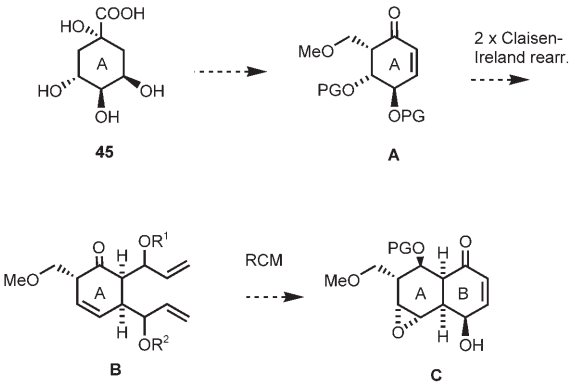
ence (indicated by vertical arrow) to give cyclohexenone derivative **61**. Reduction under Luche conditions furnished allylic alcohol **62** stereoselectively, which was converted into ester **63** under inversion of configuration. Claisen–Ireland rearrangement[16] smoothly gave acid **64** as a single stereoisomer. After reduction to alcohol **65**, the INOC annulation sequence was performed and indeed led to isoxazoline **70** in high overall yield (Schemes 17 and 18). However, all attempts to generate the desired hydroxy ketone failed. Either ether **71** was obtained (which demonstrated the proximity of functional groups in *cis*-decalin systems such as **73**) or over-reduction to **72** occurred. To rescue the approach, the double bond was protected as an acetonide in **75**. In fact, hydroxy ketone **76** was now formed without problems and protected as the triethylsilyl (TES) ether **77** (Scheme 19). However, although vinyl magnesium bromide could be



Scheme 19.



Scheme 20.



Scheme 21.

added to give **78** stereoselectively, isopropenyl magnesium bromide did not react at all.

To exploit the INOC approach further, the possibility of introducing the appendage in ring B prior to annulation was investigated (Scheme 20). Thus aldehyde **68a** was converted into adduct **80** through Crimmins aldolization[17] with oxazolidinethione **79**. Tesylation and reduction gave aldehyde **81** and after the usual INOC procedure, isoxazoline **83** was obtained. Reductive ring opening to hydroxy ketone **84** was successful; however, as extensive epimerization occurred, the INOC approach was abandoned as a whole.

Ring-Closing Metathesis (RCM) Annulation

Following the general retrosynthetic concept depicted in Scheme 21, intermediate **62** was chosen as a substrate for a Claisen–Ireland rearrangement (Scheme 22). It turned out that diol **86** could be acylated at the allylic alcohol position with high regioselectivity to give ester **88**. The remaining hydroxyl function was TES-protected and a Claisen–Ireland rearrangement was performed to give acid **90**, which was converted to olefin **93** as shown. After desilylation to **94**, an analogous sequence was performed that furnished the desired diolefin **98**.

RCM of **98** with Hoveyda's catalyst[18] gave *cis*-dehydrooctalin **99** (Scheme 23), which was converted into enone **101** with high yield. Stereo- and regioselective epoxidation of the electron-rich double bond led to epoxide **102**, diastereomerically pure according to the ^{1}H NMR spectrum (Figure 2) after chromatography, which is now ready for the addition of side chain **5**. From alkoxide **103**, the desired cyclic ether **104** should be formed.

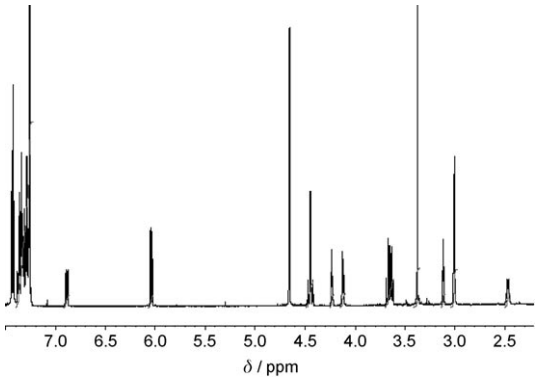
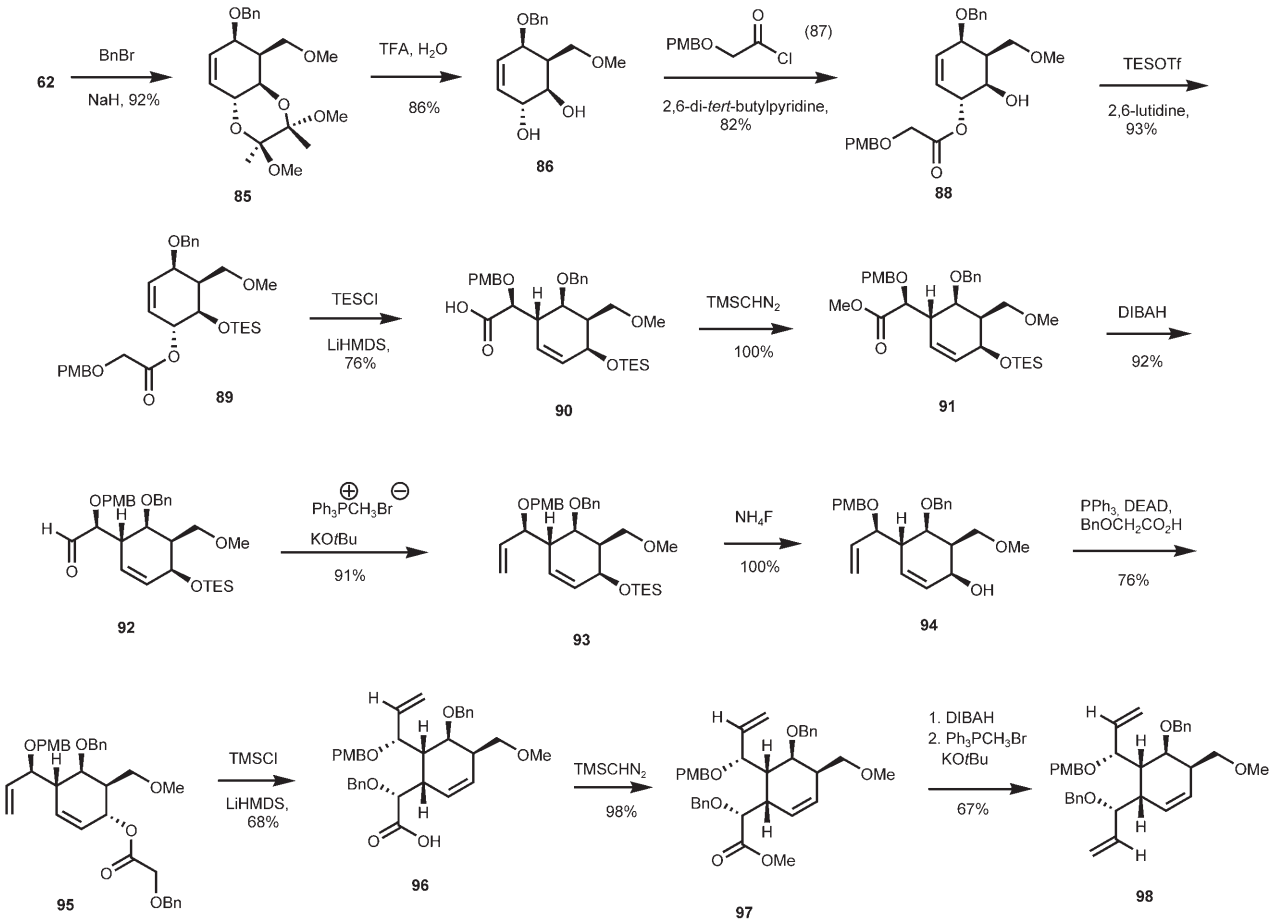


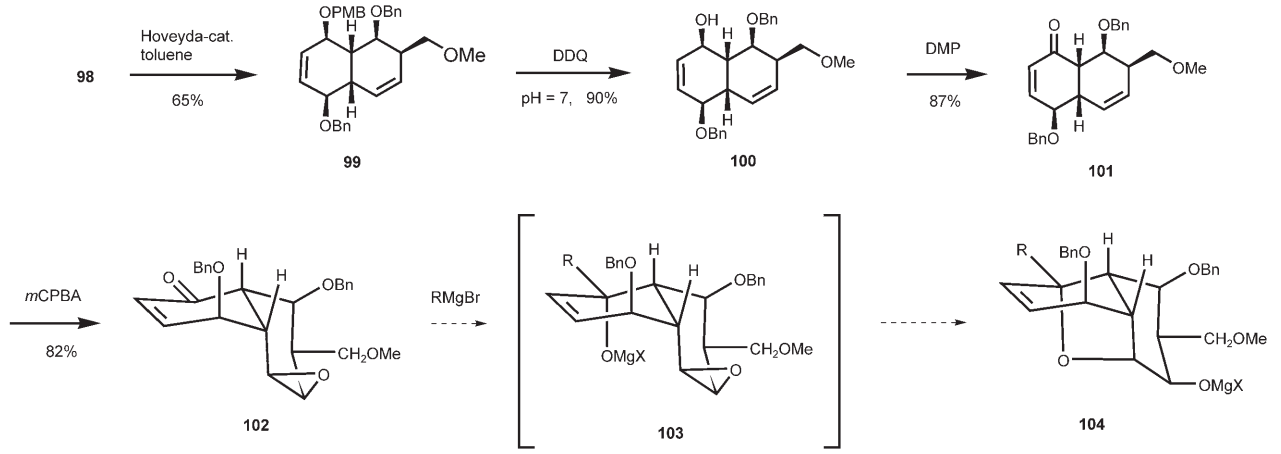
Figure 2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of epoxide **102**.

Acknowledgements

We thank the Schering AG, Berlin, for chemicals, Drs. H. Kählig and L. Brecker for NMR spectroscopic measurements, and G. Giester for the X-ray analysis of compound **43**.



Scheme 22.



Scheme 23.

[1] a) *Antibiotic Resistance: Origin, Evolution, Selection and Spread* (Eds.: D. J. Chadwick, J. Goode), Wiley, Chichester, **1997**; b) S. B. Levy, *Sci. Am.* **1998**, *278*, 46, and references therein.

[2] M. Speitling, I. Grün-Wollny, F. G. Hannske, H. Laatsch, *12 and 13 IRSEER Naturstofftage der DECHEMA e.V. Irsee*, **2000** and **2001**, poster sessions.

[3] W. D. Celmer, C. N. Chmurny, C. E. Moppett, R. S. Ware, P. C. Watts, E. B. Whipple, *J. Am. Chem. Soc.* **1980**, *102*, 4203; Review: J. Kallmerten, *Studies in Natural Products Chemistry, Vol. 17* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 283–310, and references cited therein; synthesis: D. J. Plata, J. Kallmerten, *J. Am. Chem. Soc.* **1988**, *110*, 4041; L. T. Rossano, D. J. Plata, J. Kallmerten, *J. Org. Chem.* **1988**, *53*, 5189, and references therein.

[4] a) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31; b) J. A. Marshall, X. J. Wang, *J. Org. Chem.* **1992**, *57*, 1242; c) J. A. Marshall, H. Chobanian, P. Wipf, J. Pierce, *Org. Synth.* **2005**, *82*, 43; d) M. J. C. Buckle, I. Fleming, *Tetrahedron Lett.* **1993**, *34*, 2383; e) M. J. C. Buckle, I. Fleming, S. Gil, K. L. C. Pang, *Org. Biomol. Chem.* **2004**, *2*, 749.
[5] J. W. Coe, W. R. Roush, *J. Org. Chem.* **1989**, *54*, 915.
[6] Review: M. A. J. Duncton, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1235.
[7] K. Ando, *J. Org. Chem.* **1999**, *64*, 8406.
[8] P. Soucy, A. L'Heureux, A. Toro, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 9983, and references therein; W. R. Roush, K. Koyoma, M. L. Curtin, K. J. Moriarty, *J. Am. Chem. Soc.* **1996**, *118*, 7502.
[9] A. Sorg, R. Brückner, *Synlett* **2005**, 289.
[10] Review: J. Mulzer in *Organic Synthesis Highlights, Vol. I* (Eds.: J. Mulzer, H. J. Altenbach, M. Braun, K. Krohn, H. U. Reissig), VCH, Weinheim, **1990**, p. 77.
[11] Reviews on RCM: A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012; T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4740; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592; S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900; J. Mulzer, E. Öhler, *Top. Organomet. Chem.* **2004**, *13*, 269; K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; T. Gaich, J. Mulzer, *Curr. Top. Med. Chem.* **2005**, *5*, 1473.
[12] G. Ulibarri, W. Nadler, T. Skrydstrup, H. Audrain, A. Chiaroni, C. Riche, D. Grierson, *J. Org. Chem.* **1995**, *60*, 2753.
[13] V. S. Enev, M. Drescher, H. Kählig, J. Mulzer, *Synlett* **2005**, 2227.
[14] E. J. Corey, P. B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 1979.
[15] L. M. Murray, P. O'Brien, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 1943.
[16] L. A. Paquette in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, pp. 785–898.
[17] M. T. Crimmins, J. She, *Synlett* **2004**, 1371.
[18] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168; S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973.

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