Natural Products (2)

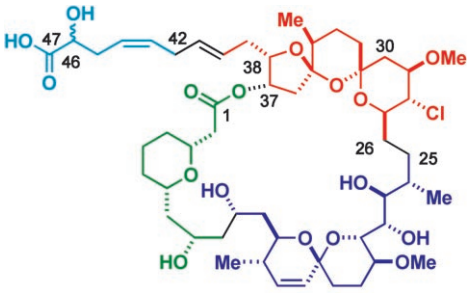
DOI: 10.1002/ange.200601655

Toward the Total Synthesis of Spirastrellolide A. Part 2: Conquest of the Northern Hemisphere**

Alois Fürstner, Michaël D. B. Fenster, Bernhard Fasching, Cédrickx Godbout, and Karin Radkowski*

The novel antimitotic agent spirastrellolide A (**1**), isolated from the Caribbean sponge *Spirastrella coccinea*, is endowed with potent and selective phosphatase inhibitory properties.[1] Although the relative stereochemistry of each individual domain embedded into the macrocyclic frame of this marine natural product has been elucidated by spectroscopic means, the relationship between these stereoclusters remains elusive and the absolute configuration of **1** is equally unknown.[1] Scheme 1 therefore depicts only one of 16 possible isomers that might represent the correct stereostructure of spirastrellolide A.

Intrigued by the exquisite structural complexity of this macrolide and the prospect of contributing to a synthesis-driven mapping of its promising biological profile,[2] we



1

Scheme 1. One of the 16 possible stereostructures that might represent spirastrellolide A. Note that the relative stereochemistry within the color-coded segments has been established, whereas the stereochemical relationship between any pair of them is still unknown.

[*] Prof. A. Fürstner, Dr. M. D. B. Fenster, Dipl.-Ing. B. Fasching, Dr. C. Godbout, K. Radkowski
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: fuerstner@mpi-muelheim.mpg.de

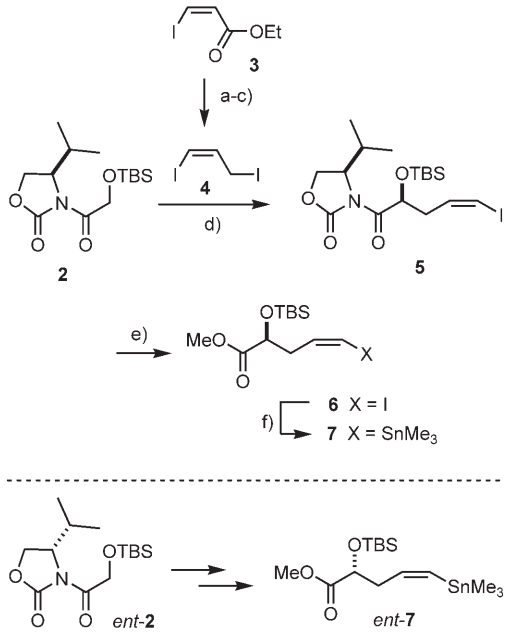
[**] Generous financial support from the MPG, the Fonds der Chemischen Industrie, the Alexander-von-Humboldt Foundation (fellowship to M.D.B.F.), and the Fonds de Recherche sur la Nature et les Technologies (Québec; fellowship to C.G.) is gratefully acknowledged. We thank Mrs B. Gabor, Mrs C. Wirtz, and Dr. R. Mynott for their invaluable help with the structural analysis of several key intermediates.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

embarked on a program aimed at the development of a flexible access route that must allow the unsolved stereochemical issues to be addressed in an unambiguous yet concise fashion. The preceding Communication outlines the overall strategy and reports the conquest of the southern hemisphere, which extends from C1 to C25 in a fully functional form.[3] Outlined below is the preparation of the complementary northern domain, which consists of the intricate chlorinated [5,6,6]-bis-spiroacetal entity and the lateral chain bearing the remote C46 chiral center of unknown configuration.[4]

In view of the potentially labile character of the skipped *E*,*Z* diene unit, it seems advisable to attach the side chain to the macrocyclic core only in the final stages of the envisaged total synthesis by a methodology that is likely compatible with the displayed array of functional groups. As palladium-catalyzed C–C bond formations should qualify for this purpose, the side-chain surrogate (fragment **A**) was designed as a vinyl stannane amenable to cross-coupling with retention of its *Z* configured double bond.

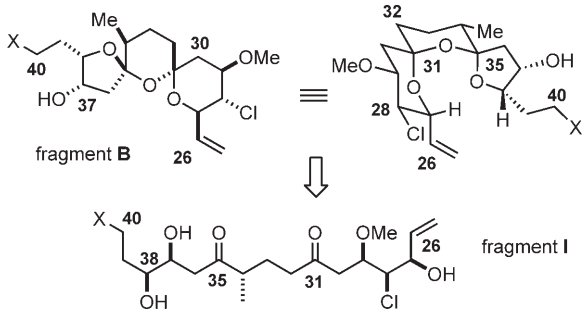
The enantioselective synthesis of **A** was based on the glycolate allylation methodology concurrently reported by Danishefsky and Crimmins (Scheme 2).[5] In the event, allylation of the sodium enolate derived from **2** with the bifunctional reagent **4**[6] effectively delivered compound **5** as a single diastereomer. Removal of the auxiliary furnished methyl ester **6** (> 99 % *ee*) in good yield,[7] which was transformed into stannane **7** by a palladium-catalyzed reaction with hexamethylditin in the presence of the Hünig base.[8]



Scheme 2. Enantioselective synthesis of fragment **A**. Reagents and conditions: a) dibal-H, THF, −78→0 °C (68 %); b) MsCl, Et_3N, CH_2Cl_2, −78 °C→RT; c) $(nBu)_4NI$, acetone (83 %; 2 steps); d) NaHMDS, THF, then iodide **4**, −78→−45 °C (87 %); e) MeOMgBr, MeOH/CH_2Cl_2, 50 °C (73 %); f) Me_6Sn_2, $[Pd(PPh_3)_4]$ (4.5 mol %), $(iPr)_2NEt$ (30 mol %), benzene, reflux (78 %). dibal-H = diisobutyl aluminium hydride, MsCl = methanesulfonyl chloride, NaHMDS = sodium hexamethyldisilazide, TBS = *tert*-butyldimethylsilyl.

This route allowed the convenient preparation of either enantiomer of **A** in multigram quantities from commercially available starting materials.

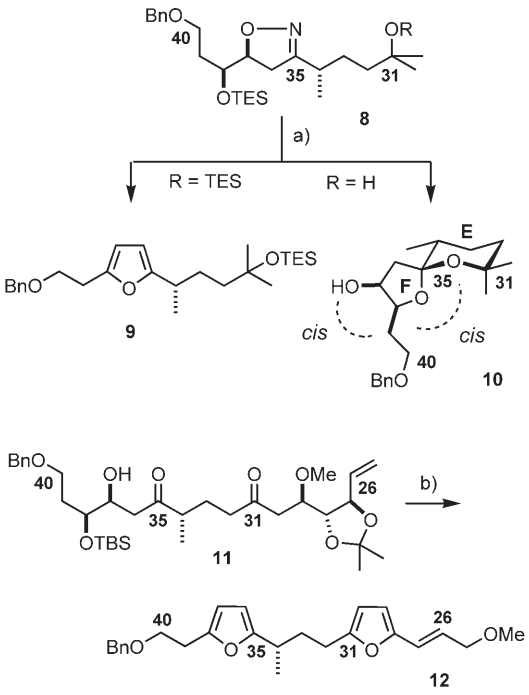
Inspection of the conspicuous bis-spiroacetal motif[9] embedded into the C26–C40 backbone of spirastrellolide A (fragment **B**) suggests that a thermodynamically controlled cyclization of a suitable acyclic precursor of type **I** should be productive as a result of the reigning double anomeric effect and the all-equatorial disposition of the substituents displayed on this particular structural motif (Scheme 3). Despite such a seemingly favorable arrangement, however, the preparation of this intriguing substructure posed significant challenges that could only be mastered after we had acquired intelligence on its chemical disposition.



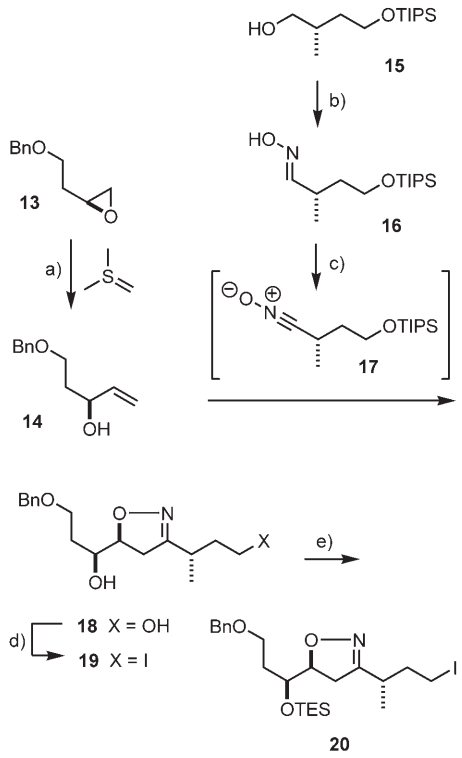
Scheme 3. Unfolding of the [5,6,6]-bis-sprioacetalic entity **B** into a linear precursor **I**; for the segment numbering see Ref. [3].

Although a detailed report on our model studies must await a forthcoming full paper, the results summarized in Scheme 4 are representative and illustrate some key observations that provided valuable guidance for the development of the successful route. Specifically, cleavage of the N–O bond in isoxazoline **8a** (R = TES)[10] with $[Mo(CO)_6]$[11] followed by attempted acetalization of the released hydroxy ketone resulted in exclusive aromatization with formation of furan **9**, even though exceptionally mild conditions were chosen. In stark contrast, however, the model gains validity if the seemingly labile TES ether protecting the tertiary alcohol at C31 is removed prior to cyclization. Under identical conditions, the reaction of **8b** (R = H) now delivers the truncated C31–C40 spirocycle **10** in an unoptimized yield of 51 %. The much more elaborate model **11**[10] is similarly instructive: treatment of this particular spirocyclization precursor bearing hydroxy groups yet to be liberated from the isopropylidene acetals with an assortment of Lewis or Bronsted acids under different experimental conditions invariably led to a complex mixture, with the bisfuran **12** being the only product that could be identified.

These results advocate the notion that a free hydroxy group at C31 must be ready to lock the incipient tetrahydrofuran ring; otherwise, aromatization, which is thought to be driven by the release of transannular strain caused by the all-*cis* orientation of the substituents on the five-membered ring (cf. compound **10**), will prevail. Therefore, it is likely that proper phasing of protecting-group cleavage versus acetal formation will be decisive for the success of the synthesis,



Scheme 4. Model studies concerning the bis-spiroacetal segment. Reagents and conditions: a) 1. $[Mo(CO)_6]$, MeCN/H_2O (5:1), 90 °C; 2. SiO_2 (**9**: 66 %; **10**: 51 %); b) catalytic amounts of CSA, PTSA, TMSOTf, aq. HCl, or $FeCl_3/SiO_2$, in MeOH, acetone, or CH_2Cl_2 (**12**: 5–35 %, see the text). CSA = camphorsulfonic acid, PTSA = *p*-toluenesulfonic acid, TMSOTf = trimethylsilyl triflate.

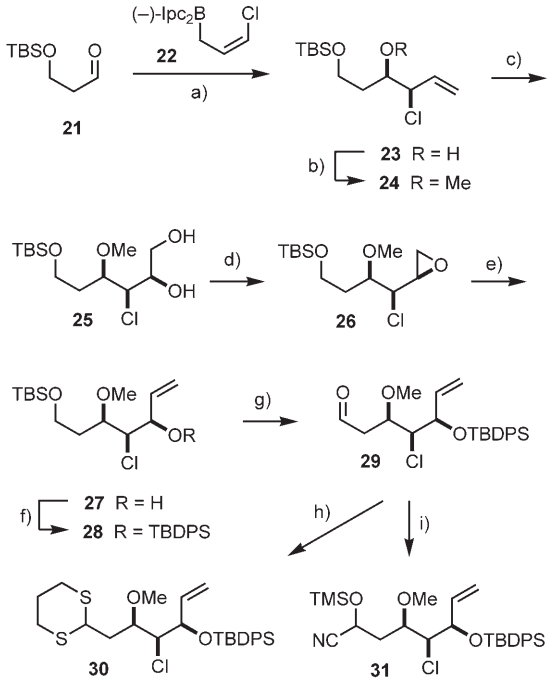


Scheme 5. Preparation of the C32–C40 segment. Reagents and conditions: a) $Me_3S^+ I^-$, *n*BuLi, THF, −10 °C→RT (84 %); b) 1. TPAP, NMO, CH_2Cl_2, MS 4 Å; 2. hydroxyamine hydrochloride, Et_3N, EtOH (78 %; 2 steps); c) 1. *t*BuOCl, −78 °C, CH_2Cl_2, then alkene **14**, EtMgBr, *i*PrOH; 2. TBAF, THF (76 %; 2 steps); d) I_2, imidazole, PPh_3, THF (83 %); e) TESOTf, 2,6-lutidine, THF (92 %). MS = molecular sieves, NMO = *N*-methyl-morpholine-*N*-oxide, TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl, TIPS = triisopropylsilyl, TPAP = tetra-*n*-propylammonium perruthenate.

whereas extensive equilibration must be avoided during attempted spirocyclization. Hence, we concluded that the synthesis of the northern hemisphere should not rely on thermodynamic but rather kinetic control.

In response to this analysis, the convergent route to the cyclization precursor summarized in Schemes 5–8 was designed. Thus, transformation of the known alcohol **15**[12] to oxime **16** followed by exposure to *t*BuOCl[13] at low temperature gave nitrile oxide **17** (Scheme 5), which underwent a smooth 1,3-dipolar cycloaddition[14] with the magnesium salt of alcohol **14** under conditions originally described by Kanemasa et al.[15] The required olefin **14** was conveniently prepared in enantiopure form by hydrolytic kinetic resolution[16] of *rac*-**13** followed by reaction of the resulting optically pure epoxide (*S*)-**13** with dimethylsulfonium methylide.[17] The outcome of the cycloaddition reaction developed by Kanemasa et al.[15] was highly rewarding, thus exclusively furnishing the *syn*-configured 2-isoxazoline **18** in 76 % yield on a multigram scale after fluoride-induced cleavage of the terminal TIPS ether to facilitate purification. Regioselective conversion of the primary hydroxy group in **18** into the corresponding iodide **19** followed by silylation of the remaining secondary alcohol provided the suitably protected C32–C40 surrogate **20** in excellent overall yield. As mentioned above, all steps that led to this valuable building block were scalable and are therefore considered highly adequate.

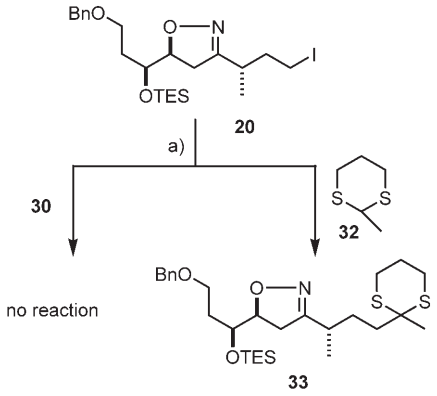
The preparation of the required coupling partner (Scheme 6) commenced with an asymmetric chloroallylation of aldehyde **21**, a variant of Brown's reliable method developed by Oehlschlager and co-workers.[18] The reaction afforded chlorohydrine **23** in good yield with virtually quantitative *syn* selectivity and respectable optical purity (93 % *ee*) and could be performed on a > 11-g scale, provided that the reagent **22** was generated from freshly prepared (−)-$(ipc)_2$BOMe (icp = isopinocampheyl).[19] Methylation of alcohol **23** followed by asymmetric dihydroxylation[20] of the resulting product **24** gave diol **25**[4] in 73 % yield over both steps. Compound **25** was then converted into epoxide **26** by reaction with tosyl chloride and treatment of the resulting crude sulfonate with K_2CO_3 in MeOH. As in the case of **13** described above, homologation of this epoxide with dimethylsulfonium methylide in THF led to the desired allylic alcohol **27** in 92 % yield, thus attesting to the excellent application profile of this valuable transformation.[17] This particular example is quite challenging because the alkoxide primarily formed upon opening of the oxirane by the nucleophile can undergo an intramolecular nucleophilic substitution of the adjacent chlorine center with formation of a new epoxide ring. This undesirable pathway, however, could be suppressed by using an excess of the sulfur ylide and quenching of the mixture at low temperature after a reaction time of only 10 minutes. Attachment of a TBDPS group to the allylic alcohol in **27**, removal of the more labile primary TBS



Scheme 6. Preparation of the C26(25)–C31 segment. Reagents and conditions: a) Et_2O, −78 °C (85%; 93% *ee*); b) Me_3OBF_4, proton sponge (86%); c) [OsO_4] (1 mol%). $K_3Fe(CN)_6$, $(DHQ)_2Pyr$ (2.5 mol%), *t*BuOH/H_2O (85%); d) 1. tosyl chloride, pyridine; 2. K_2CO_3, MeOH (73%; 2 steps); e) $Me_3S^+ I^-$, *n*BuLi, THF, 0 °C (92%); f) TBDPSCl, imidazole (quant.); g) 1. PPTS cat., MeOH (96%); 2. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C→RT (96%); h) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (86%); i) TMSCN, NMO, CH_2Cl_2 (82%). DMSO = dimethyl sulfoxide, $(DHQ)_2Pyr$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, PPTS = pyridinium *p*-toluene sulfonate, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TMSCN = trimethylsilanecarbonitrile.

ether in **28**, and oxidation of the resulting alcohol afforded aldehyde **29**, which is amenable to "umpolung" alkylation with iodide **20**.

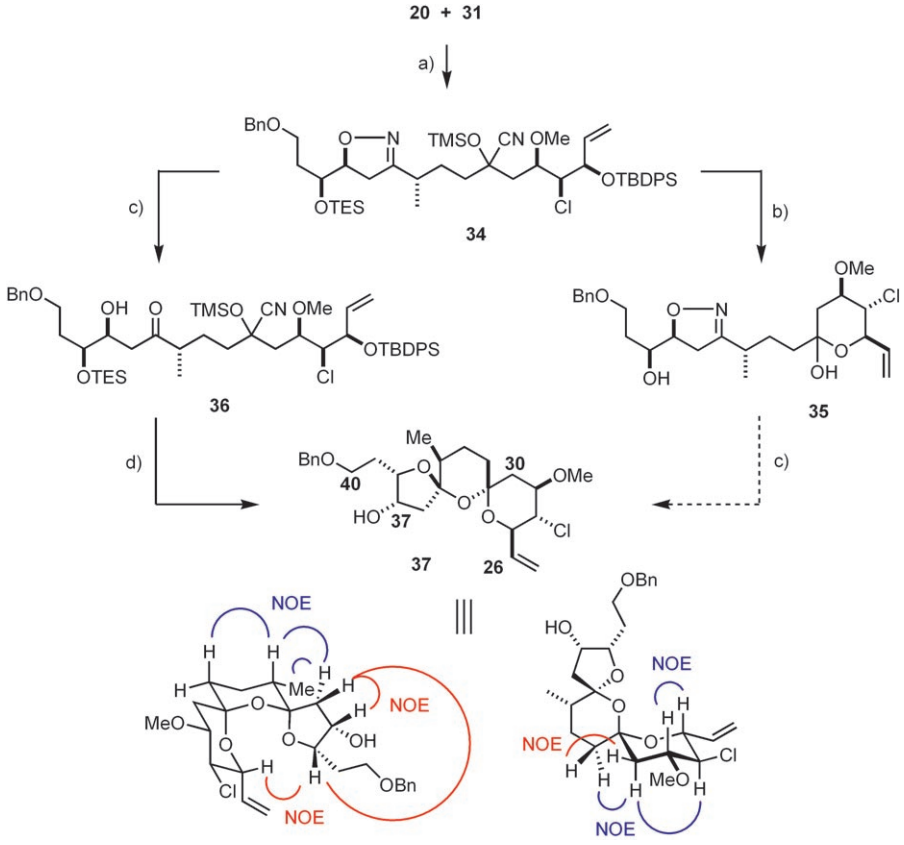
Although a model study (Scheme 7) showed that **20** undergoes a high-yielding alkylation with deprotonated dithiane **32**, all attempts to engage the much more elaborate dithiane **30** (Scheme 6) derived from aldehyde **29** met with failure. Deuteration experiments indicated that it was the deprotonation step that did not occur even though various bases and fairly forcing conditions were applied. Although these puzzling results require further investigation, they must be seen in the light of a report that suggested that tethered olefins can substantially alter the kinetic acidity of a dithiane by through-space orbital interactions ($\pi \rightarrow \sigma^*$ donation).[21] Under this premise, we considered that the use of a cyanohydrin rather than a



Scheme 7. Model study. Reagents and conditions: a) Compound **32**, *n*BuLi, $(n\text{Bu})_2Mg$, THF, RT; then iodide **20**, −78 °C (**33**: 87%).

dithiane might be advantageous for the envisaged "umpolung" alkylation, as the deprotonation step should be easier because of the enolate character of the resulting reactive intermediate.[22]

This plan could be reduced to practice as shown in Scheme 8. Exposure of aldehyde **29** to TMSCN and NMO[23] readily furnished cyanohydrin **31** (Scheme 6), which was deprotonated with LDA at low temperature and treated with iodide **20** to give the desired product **34** in respectable yield



Scheme 8. Assembly of the northern hemisphere of spirastrellolide A. Reagents and conditions: a) LDA, THF, −78 °C (52%); b) TASF, aq. DMF (**35**: 99%); c) [$Mo(CO)_6$], MeCN/H_2O, 90 °C (**36**: 66%); d) 1. TASF, aq. DMF; 2. PPTS cat., CH_2Cl_2 (**37**: 96%; d.r. = 4.1:1.7:1; see text). DMF = dimethylformamide, LDA = lithium diisopropyl amide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

(52%; 73% based on recovered starting material)[24] as a single diastereomer.[25] With **34** in hand, the stage was set for the final spirocyclization.

With the information gathered in the model studies in mind (see above), **34** was first subjected to exhaustive desilylation with TASF in aqueous DMF,[26] which resulted in the quantitative formation of hemiacetal **35**. Unfortunately, however, cleavage of the remaining N–O bond in **35** with the aid of $[Mo(CO)_6]$[11] was prohibited by the presence of the free alcohols. Therefore, the order of events was inverted, thus starting with the reductive cleavage of the isoxazoline unit in **34** followed by treatment of the resulting product **36** with TASF,[26] which simultaneously removed the silyl ethers and unmasked the ketone from the cyanohydrin precursor. It was gratifying to see that stirring of the trihydroxy diketone,[27] thus formed with catalytic amounts of PPTS in CH_2Cl_2, triggered an almost quantitative bis-spirocyclization event and delivered the desired product **37** together with two minor isomers in a 96% yield of the combined products with a diastereomeric ratio of 4.1:1.7:1. No furan formation was detected under these conditions. Routine flash chromato graphy allowed the isolation of **37** in respectable 61% yield in analytically pure form; this compound represents the intact and suitably protected northern half of spirastellolide A. Detailed spectroscopic analyses leave no doubt about its constitution and relative configuration. Most characteristic are the strong NOE interactions (indicated in Scheme 8) that reflect the doubly anomeric bis-spiroacetal substructures and the coupling constants that confirm the all-equatorial orientation of the substituents residing on the pyranose rings (see the Supporting Information).

In summary, this investigation outlines a reliable approach to the northern hemisphere of spirastrellolide A (**1**); as the complementary southern domain has also been obtained,[3] the entire carbon frame of this remarkably complex marine macrolide is now covered. Nevertheless, we are well aware that this venture is no more but an auspicious start for the conquest of this challenging natural product because of the as of yet unanswered stereochemical issues delineated in the introduction. Undaunted, however, we are now actively pursuing possible end games with the hope of reaching this monumental target soon.

Received: April 26, 2006

Keywords: cycloaddition · macrolides · natural products · phosphatase inhibitors · total synthesis

[1] a) D. E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberge, R. J. Andersen, *Org. Lett.* **2004**, *6*, 2607 – 2610; b) D. E. Williams, M. Roberge, R. Van Soest, R. J. Andersen, *J. Am. Chem. Soc.* **2003**, *125*, 5296 – 5297.

[2] For previous syntheses and biological evaluations of phosphatase inhibitors from this group, see: a) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Angew. Chem.* **2003**, *115*, 5519 – 5522; *Angew. Chem. Int. Ed.* **2003**, *42*, 5361 – 5364; b) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Tetrahedron* **2004**, *60*, 9543 – 9558; c) A. Fürstner, J. Ruiz-Caro, H. Prinz, H. Waldmann, *J. Org. Chem.* **2004**, *69*, 459 – 467; d) A. Fürstner, K. Reinecke, H. Prinz, H. Waldmann, *ChemBioChem* **2004**, *5*, 1575 – 1579; e) M. Manger, M. Scheck, H. Prinz, J. P. von Kries, T. Langer, K. Saxena, H. Schwalbe, A. Fürstner, J. Rademann, H. Waldmann, *ChemBioChem* **2005**, *6*, 1749 – 1753.

[3] A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout, K. Radkowski, *Angew. Chem.* **2006**, *118*, 5632 – 5636; *Angew. Chem. Int. Ed.* **2006**, *45*, 5506 – 5510.

[4] The only other synthesis of the [5,6,6]-bis-spirocyclic entity of **1**: I. Paterson, E. A. Anderson, S. M. Dalby, O. Loiseleur, *Org. Lett.* **2005**, *7*, 4121 – 4224.

[5] a) M. D. Chappell, S. J. Stachel, C. B. Lee, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 1633 – 1636; b) M. T. Crimmins, K. A. Emmitte, J. D. Katz, *Org. Lett.* **2000**, *2*, 2165 – 2167.

[6] Prepared according to literature precedence: a) S. Ma, X. Lu, Z. Li, *J. Org. Chem.* **1992**, *57*, 709 – 713; b) E. Piers, J. Renaud, S. J. Rettig, *Synthesis* **1998**, 590 – 602; c) A. Toró, P. Nowak, P. Deslongchamps, *J. Am. Chem. Soc.* **2000**, *122*, 4526 – 4527.

[7] D. A. Evans, M. M. Morrissey, R. L. Dorow, *J. Am. Chem. Soc.* **1985**, *107*, 4346 – 4348; good results were obtained only when the reaction was performed at 50 °C; otherwise, a competing attack of MeOMgBr at the carbamate carbonyl group of the substrate is observed, which lowers the yield of **6**.

[8] a) W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033 – 3040; b) W. D. Wulff, G. A. Peterson, W. E. Bauta, K.-S. Chan, K. L. Faron, S. R. Gilbertson, R. W. Kaesler, D. C. Young, C. K. Murray, *J. Org. Chem.* **1986**, *51*, 277 – 279; c) C. D. Vanderwal, D. A. Vosburg, E. J. Sorensen, *Org. Lett.* **2001**, *3*, 4307 – 4310.

[9] Review on bis-spiroacetal formations: M. A. Brimble, F. A. Farès, *Tetrahedron* **1999**, *55*, 7661 – 7706.

[10] Details will be reported in a forthcoming full paper.

[11] a) A. Guarna, A. Guidi, A. Goti, A. Brandi, F. De Sarlo, *Synthesis* **1989**, 175 – 178; b) P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, *Synthesis* **1987**, 276 – 278.

[12] J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410 – 6424.

[13] M. J. Mintz, C. Walling, *Org. Synth.* **1969**, *49*, 9 – 12.

[14] Reviews on the use of 2-isoxazolines as aldol surrogates: a) D. P. Curran, *Adv. Cycloaddit.* **1988**, *1*, 129 – 189; b) S. Kanemasa, O. Tsuge, *Heterocycles* **1990**, *30*, 719 – 736.

[15] a) S. Kanemasa, M. Nishiuchi, A. Kamimura, K. Hori, *J. Am. Chem. Soc.* **1994**, *116*, 2324 – 2339; b) for an optimization and elegant application, see: J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem.* **2001**, *113*, 2128 – 2131; *Angew. Chem. Int. Ed.* **2001**, *40*, 2082 – 2085.

[16] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307 – 1315.

[17] L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. Le Gall, D.-S. Shin, J. R. Falck, *Tetrahedron Lett.* **1994**, *35*, 5449 – 5452.

[18] a) S. Hu, S. Jayaraman, A. C. Oehlschlager, *J. Org. Chem.* **1998**, *63*, 8843 – 8849; b) S. Hu, S. Jayaraman, A. C. Oehlschlager, *J. Org. Chem.* **1996**, *61*, 7513 – 7520.

[19] U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401 – 404.

[20] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483 – 2547.

[21] A. B. Smith, C. M. Adams, *Acc. Chem. Res.* **2004**, *37*, 365 – 377.

[22] a) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286 – 5287; b) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1974**, *96*, 5272 – 5274; c) for applications in natural product synthesis, see: T. Takahashi, H. Nemoto, Y. Kanda, J. Tsuji, Y. Fukazawa, T. Okajima, Y. Fujise, *Tetrahedron* **1987**, *43*, 5499 – 5520; d) H. Takayanagi, Y. Kitano, Y. Morinaka, *J. Org. Chem.* **1994**, *59*, 2700 – 2706; e) A. B. Smith, C. Sfouggatakis, D. B. Gotchev, S. Shirakami, D. Bauer, W. Zhu, V. A. Doughty, *Org. Lett.* **2004**, *6*, 3637 – 3640.

[23] S. S. Kim, G. Rajogopal, D. W. Kim, D. H. Song, *Synth. Commun.* **2004**, *34*, 2973 – 2980.

[24] The time for deprotonation must be < 5 minutes; otherwise, significant decomposition of the cyanohydrin part was observed. Likewise, the use of KHMDS as the base and hexamethyl phosphoramide (HMPA) as a cosolvent were detrimental.
[25] The configuration of the cyanohydrin center C31 has not been determined.
[26] a) K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436 – 6437; b) R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1983**, *105*, 1598 – 1608; c) recent application: C. Aïssa, R. Riveiros, J. Ragot, A. Fürstner, *J. Am. Chem. Soc.* **2003**, *125*, 15512 – 15520.
[27] NMR spectroscopic analysis suggests that the compound mainly exists as a pyranoid hemiacetal analogous to that found in **35**.

