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Total Synthesis of (−)-Spirotryprostatin B: Synthesis and Related Studies

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Abstract: The total synthesis of spirotryprostatin B, a cytostatic spiro[pyrrolidine-3,3′-oxindole] alkaloid, is described. The key step of the synthetic approach consists of the application of the MgI_2-mediated ring-expansion reaction of a spiro[cyclopropane-1,3′-oxindole] with an aldimine, leading to rapid assembly of the spirotryprostatin core. The route documents the installation of the prenyl side chain by Julia−Kocieński olefination of a key aldehyde precursor, a transformation that ultimately allows for facile synthesis of analogues and facilitates structure−activity relationships studies

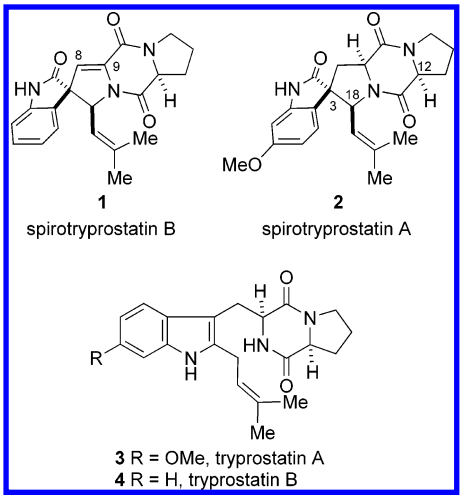
Introduction

In 1996, Osada and co-workers reported the isolation of spirotryprostatin B (**1**) together with spirotryprostatin A (**2**) by fermentation of *Aspergillus fumigatus* BM939 (Chart 1).[1] From 400 L of fermentation broth, only 11 mg of **1** and 1 mg of **2** were obtained. Both compounds were shown to inhibit the cell cycle in the G2/M phase with half-maximal inhibitory concentrations (MIC) of 197.5 and 14.0 μM for **2** and **1**, respectively. Spirotryprostatin B (**1**) also inhibits the growth of human chronic myelogenous leukemia K562 cells and human promyelocytic leukemia HL-60 cells with MICs of 35 and 10 μg mL^{-1}, respectively.

The significantly enhanced inhibitory activity displayed by **1** when compared to that of **2** was speculated to be related to the absence of the 6-methoxy group on the oxindole ring. A similar observation was made for the structurally related compounds tryprostatin A (**3**) and B (**4**), wherein **4** is also observed to possess greater activity than **3** (Chart 1).[2]

Structural elucidation of spirotryprostatins A and B was effected through the use of a combination of analytical methods: HR-EI-MS, IR, and NMR. Analysis of the IR spectrum suggested the presence of a diketopiperazine and a lactam ring fused onto an aromatic ring. The findings were consistent with the analysis of the ^{13}C NMR spectra. Deduction of partial structures was enabled by detailed analysis of the ^{1}H and ^{13}C NMR spectra using ^{1}H−^{1}H COSY, PFG-HMQC, and NOE difference experiments. The connectivity between these fragments could be established by PFG-HMBC. Assignment of the relative stereochemistry at C3 and C18 (spirotryprostatin numbering) was possible by NOE. The relative configuration at C12 could only be determined for spirotryprostatin A (**2**), but it was assumed to be identical for spirotryprostatin B (**1**),

Chart 1. Structures of Spirotryprostatin- and Tryprostatin Natural Products

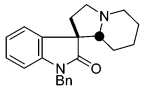
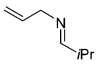
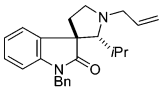
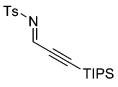
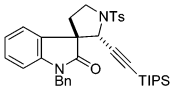
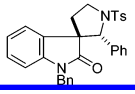


as the biogenesis of both compounds is probably similar. The absolute configuration of the natural product could not be determined, but it was assumed that the spirotryprostatins are metabolites derived from L-tryptophan and L-proline.

The spirotryprostatin skeleton is characterized by (i) a unique spiro-fusion to a pyrrolidine at the 3-position of the oxindole core, (ii) the annulated diketopiperazine ring, and (iii) a prenyl appendage. The difficulties associated with the isolation of significant quantities of **1** and **2** as well as the complex architectural features of these natural products render the spirotryprostatins compelling synthetic targets. Several groups have successfully completed total syntheses of **1** and **2**. The reports offer distinct strategies to the spiro[pyrrolidine-3,3′-oxindole] ring system.[3] The first synthetic route to the spirotryprostatin skeleton was accomplished by Danishefsky and co-workers.[4] Formation of the spiro[pyrrolidine-3,3′-oxindole] core

(1) (a) Cui, C. B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832−835. (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651−12666.
(2) Cui, C. B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527−533.
(3) For a review see: Lindel, T. *Nachr. Chem.* **2000**, *48*, 1498−1501.

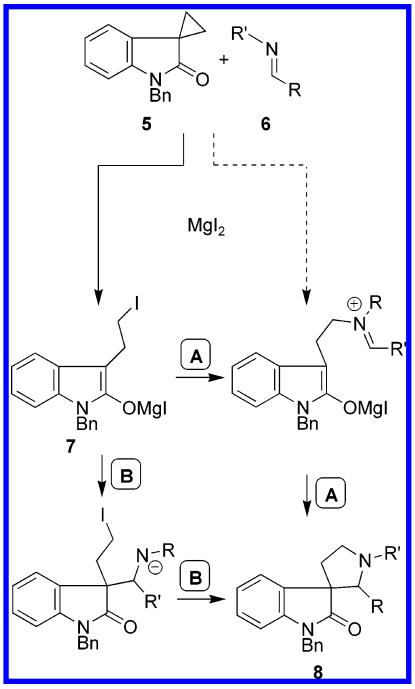
Table 1. Annulation Reaction of Imines and Cyclopropylspirooxindoles

Entry	Imine **6**	Reaction Time	Major Product	dr	Yield
1		19 h		86:14	68%
2		20 h		80:20	83%
3		4 h		98:2	77%
4		8 h		91:9	97%

in this synthesis of spirotryprostatin A was achieved through oxidative rearrangement of a tetrahydrocarboline.[5] A highly stereoselective [1,3]-dipolar cycloaddition reaction was used by Williams in his elegant total synthesis of **1**.[6] Danishefsky's synthesis of spirotryprostatin B involved a Mannich reaction of L-tryptophan-derived oxindole and 3-methylcrotonaldehyde.[7] Resolution and isolation of the desired diasteromer is carried out at a late stage in this short and efficient total synthesis, allowing for preparation of significant quantities of **1**. The synthesis of spirotryprostatin B as carried out by Wang and Ganesan also employed an oxidative rearrangement sequence.[8] Overman and Rosen successfully assembled **1** via asymmetric Heck cyclization followed by trapping of the η^3-allylpalladium intermediate by a nitrogen nucleophile.[9] Fuji et al. assembled the spiro[pyrrolidine-3,3′-oxindole] from a chiral oxindole derivative obtained from asymmetric nitroolefination.[10] More recently, in one of the shortest approaches to spirotryprostatin B, Horne showcased a stereoselective intramolecular *N*-acyliminium ion spirocyclization of a 2-halotryptophan ester derivative.[11]

We have recently developed a novel approach applicable to the spiro[pyrrolidine-3,3′-oxindole] core of spirotryprostatin by employing MgI_2-catalyzed ring-expansion of a spiro[cyclopropyl-1,3′-oxindole]and an aldimine.[12] We have shown that both *N*-alkyl- and *N*-sulfonyl aldimines participate in the annulation reaction. The products **8** of the ring-expansion reaction of spiro[cyclopropyl-1,3′-oxindole] **5** with imines **6** are obtained in high yields and good diastereoselectivities (Table 1). In our working mechanistic hypothesis, MgI_2 acts as a bifunctional catalyst where the Lewis acidic metal center and the nucleophilic iodide

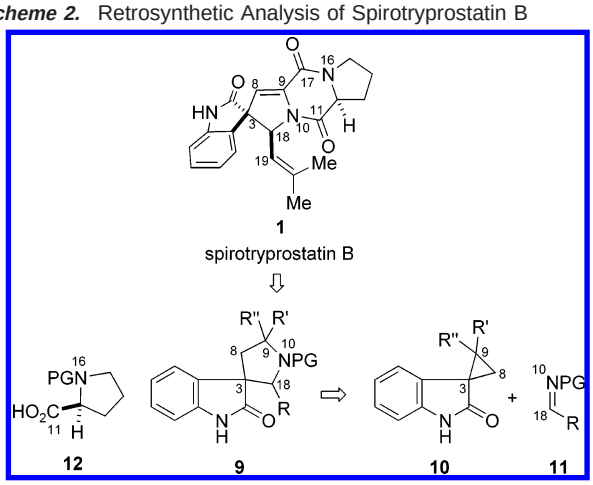
Scheme 1. Ring-Expansion Reaction of Spiro[cyclopropyl-1,3′-oxindole], **5**, with Imines **6** and Possible Mechanistic Pathways



operate in synergy, leading to opening of the cyclopropyl ring (Scheme 1). As an alternative, opening of the cyclopropyl ring directly by an imine is possible. However, the occurrence of intermediate **7** is consistent with our working hypothesis and the observation that the reaction is considerably faster with MgI_2, possessing the more nucleophilic iodide counterion, as compared to the reactions attempted with $MgBr_2$ and with $Mg(OTf)_2$, wherein no product formation was observed.[13] From the ring-opened intermediate **7** two pathways which converge onto the same product can be envisioned: (1) iodide displacement by the imine and subsequent Mannich ring closure (path **A**) and (2) addition of the oxindole enolate to C═N electrophile followed by ring closure (path **B**). The observation that the annulation can be conducted with both *N*-alkyl- and *N*-sulfonyl imines is consistent with both pathways **A** and **B**. It is likely that the first of these mechanistic pathways (**A**) is operative for *N*-alkylimines,[14−16] and by contrast, with more electrophilic

(4) (a) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138−1140. (b) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147−2155.
(5) Stahl, R.; Borschberg, H. J. *Helv. Chim. Acta* **1994**, *77*, 1331−1345.
(6) (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666−5667. (b) Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311−6322.
(7) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175−2178.
(8) Wang, H. S.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 4685−4693.
(9) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599.
(10) Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249−251.
(11) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5357−5360.
(12) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186−3189.
(13) We were able to isolate 3-(2-iodo-ethyl)-*N*-benzyl-oxindole (characterized by ^{1}H NMR and high-resolution MALDI-MS), resulting from quenching of **7** with water in a reaction wherein the imine decomposed.
(14) The ring closure of iminium (pathway **A**) is a disfavored 5-*endo-trig* cyclization process: (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846−3852. (c) Johnson, D. D. *Acc. Chem. Res.* **1996**, *26*, 476−482.
(15) A couple of examples for disfavored 5-*endo-trig* cyclization reactions are known in the literature for the formation of pyrrolidines: (a) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc. Chem. Commun.* **1980**, 648−650. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455−4458. Padwa, A.; Norman, B. H. *J. Org. Chem.* **1990**, *55*, 4801−4807. (c) Jones, A. D.; Knight, D. W. *Chem. Commun.* **1996**, 915−916. (d) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Chem. Commun.* **1997**, 2141−2142. (e) Craig, D.; Jones, P. S.; Rowlands, G. J. *Synlett* **1997**, 1423−1425. (f) Dell'Erba, C.; Mugnoli, A.; Novi, M.; Pani, M.; Petrillo, G.; Tavani, C. *Eur. J. Org. Chem.* **2000**, 903−912. (g) Chang, K. T.; Jang, K. C.; Park, H. Y.; Kim, Y. K.; Park, K. H.; Lee, W. S. *Heterocycles* **2001**, *55*, 1173−1179.
(16) A couple of examples for disfavored 5-*endo-trig* cyclization reactions are known in the literature for the formation of tetrahydrofuranes: (a) Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695−698. (b) Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron Lett.* **1995**, *36*, 7531−7534. (c) Craig, D.; Ikin, N. J.; Mathews, N.; Smith, A. M. *Tetrahedron* **1999**, *55*, 13471−13494.

Scheme 2. Retrosynthetic Analysis of Spirotryprostatin B



imines such as *N*-arylsulfonyl-protected imines, the reaction is likely to proceed through pathway **B**.

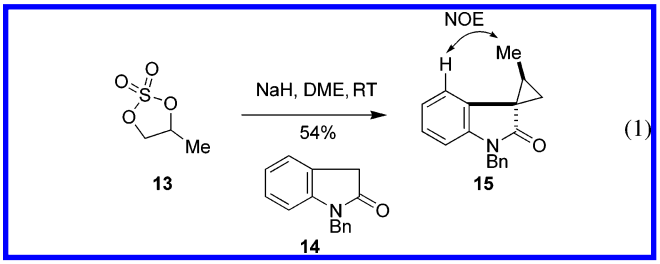
Since our initial report of the annulation reaction, a number of groups, most notably that of Lautens, have cleverly expanded the use of the annulation reaction to generate libraries of five- and six-membered heterocycles[17] and substituted pyrrolidines[18] from cyclopropyl ketones. We have showcased the application in a synthesis of both spiro[pyrrolidine-3,3′-oxindole] alkaloids, (±)-horsfiline[19] and strychnofoline.[20] In the former, we examined the possibility of generating the formaldehyde-derived *N*-methyl imine from the corresponding triazine, and in the latter we investigated stereochemical issues when a 3,4-disubstituted 2,3,4,5-tetrahydropyridine was employed as the imine partner.

Retrosynthetic Analysis and Initial Model Studies

Given the scarcity of natural spirotryprostatin B, a strategy for its total synthesis could provide significant quantities of synthetic material for further biological studies. Additionally, such a synthesis could also provide facile access to analogues (stereoisomers and structurally distinct) with which to establish structure−activity relationships of the pharmacophore and in principle lead to the identification of compounds displaying potentially enhanced biological activity.

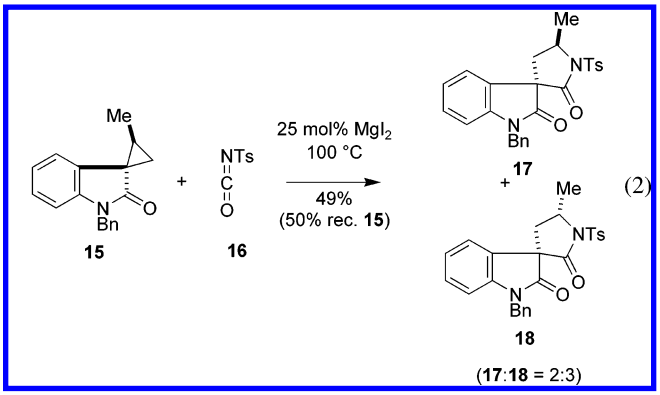
We embarked on the development of a synthesis of spirotryprostatin B driven by our interest in devising a convenient approach to the natural product. Of additional significance, the structural complexity of the spiro[pyrrolidine-3,3′-oxindole] core of spirotryprostatin presented the opportunity to test the annulation reaction of imines and spiro[cyclopropyl-1,3′-oxindoles] as an approach to systems bearing additional substitution on the pyrrolidine ring. This key issue had been left unaddressed in earlier studies by us and others. If a C-9 substituted spiro-[pyrrolidine-3,3′-oxindole] such as **9** could be accessed using the Mg(II)-catalyzed annulation reaction, convenient access to the spirotryprostatin B core could be envisioned (Scheme 2). In this respect, it is important to note that in previous reactions of unsubstituted spiro[cyclopropyl-1,3′-oxindole] **5** with aldimines **6** (Table 1), the major diastereomer always possessed the relative configuration that is observed in spirotryprostatin B (**1**) at C-3 and C-18. We anticipated preparing the key intermediate **9** from ring expansion of spiro[cyclopropyl-1,3′-oxindole] **10** and imine **11**. The substituents R, R′, and R″ as well as the protecting group (PG) on the imine nitrogen would collectively have to fulfill a number of requirements: (i) they must be compatible with the conditions of the ring-expansion reaction, (ii) they must conspire to effect annulation with good regiocontrol, and (iii) the substituent R of imine **11** should be either the prenyl moiety itself or its synthetic equivalent. Given the potential for the generation of analogues differing in the nature of the C-18 side chain, an intermediate which would allow for suitable introduction late in the route would be desirable (Scheme 2).

The first issue that would have to be examined in the implementation of the annulation reaction in the spirotryprostatin synthesis would be the regioselectivity of the ring opening. To investigate this aspect of the reaction, methyl-substituted spiro-[cyclopropyl-1,3′-oxindole] **15** was chosen. Reaction of **14** with known cyclic sulfate **13**[21] afforded **15**. Methyl-substituted spiro-[cyclopropyl-1,3′-oxindole] **15** is the major isomer of this reaction (dr 16:1). The assignment of the relative configuration was established by difference NOE experiments (eq 1).



(1)

Spiro[cyclopropyl-1,3′-oxindole] **15** was first subjected to ring-expansion conditions with *N*-*p*-tosyl-benzylidene-imine. Although the annulation products were isolated in good yields, separation of the isomeric products proved difficult, and moreover, the regio- and diastereoselectivity of the cyclopropane-fragmentation/ring-expansion reaction was difficult to ascertain. To address the issue of the regiochemical outcome, the ring expansion with *p*-tosyl-isocyanate (**16**) was carried out (eq 2).



(2)

Analysis of the reaction products was expected to be more facile because the products of the ring expansion with isocyanate **16** would possess only two stereogenic centers. When the reaction

(17) Lautens, M.; Han, W. S. *J. Am. Chem. Soc.* **2002**, *124*, 6312−6316.
(18) (a) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3147−3150. (b) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 4333−4336.
(19) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175−1181.
(20) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826−14827.
(21) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539. (b) Burgess, K.; Ho, K. K.; Ke, C. Y. *J. Org. Chem.* **1993**, *58*, 3767−3768.

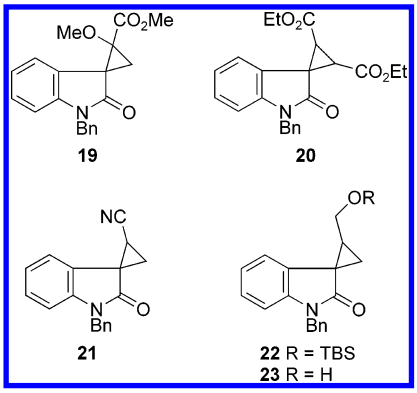


Figure 1. Spiro[cyclopropyl-1,3′-oxindoles] resistant to ring-expansion conditions in the presence of *N*-*p*-tosyl-benzylidene-imine (**27**).

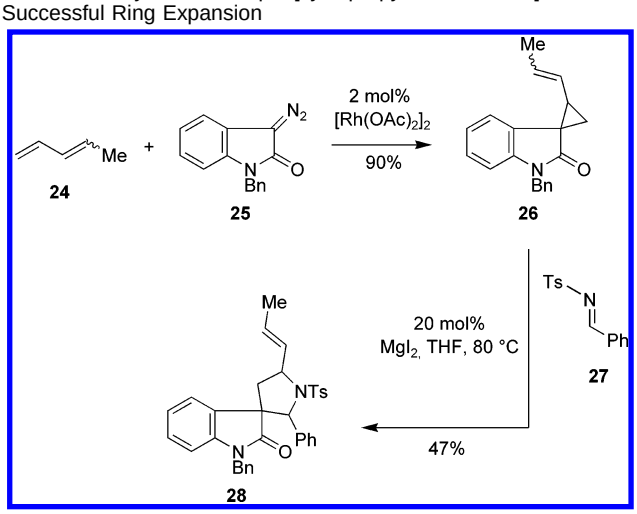
was conducted with 25 mol% MgI_2 in THF at 100 °C, products **17** and **18** were obtained as a 2:3 ratio of diastereomers. The structure of the products could be established unambiguously by X-ray crystallographic analysis of each diastereomer.[22] Interestingly, the regiochemical outcome of the reaction was rather unexpected. The observed products are consistent with highly regioselective opening of the spirofused cyclopropane, leading to cleavage of the more highly substituted C−C bond of the cyclopropyl ring.

The results of the investigations involving **15** + **16** suggest that spiro[cyclopropyl-1,3′-oxindoles] undergo highly regioselective opening under the conditions of the annulation. This finding is in accordance with Danishefsky's earlier observations involving the regioselective opening of cyclopropanes doubly substituted with activating groups, which was explained by invoking a transition-state structure with substantial polar character in the course of ring opening.[23,24] The fact that this regioselectivity is observed for a singly activated system such as **15** bodes well for further applications of these systems.

We next examined the use of substituted spiro[cyclopropyl-1,3′-oxindoles] incorporating functional groups that would permit efficient construction of the spirotryprostatin B core. The cyclopropyl derivatives **19**−**23** were prepared and tested in the ring expansion with *N*-*p*-tosyl-benzylidene-imine (Figure 1).[25,26] However, in none of the test reactions with these substrates could a spiro[pyrrolidine-3,3′-oxindole] be isolated, and the spiro-[cyclopropyl-1,3′-oxindoles] were recovered unchanged.

Our observations with **19**−**23** led us to speculate that it is necessary to have the substitution pattern of the cyclopropyl ring reinforce the polarization of the oxindole core for reaction to proceed under the conditions we have investigated.[27] In this respect, we hypothesized that a vinyl cyclopropane would be suited for participation in the ring-expansion process. Furthermore, the carbon−carbon double bond could provide an appropriate handle for subsequent installation of the C-9 carboxylate. Spiro[cyclopropyl-1,3′-oxindole] **26** was prepared from **25** and commercially available piperylene (**24**) (Scheme 3).[28] In accordance with published work, the cyclopropanation proved regioselective and occurred at the least substituted double bond. In a study on the regioselectivity of catalytic cyclopropanation of monosubstituted dienes, Doyle showed that cyclopropanation of 1-substituted dienes such as piperylene takes place at the more accessible, terminal double bond with good to excellent regioselectivity in the presence of different transition-metal catalysts including $[Rh(OAc)_2]_2$.[29] Reaction of spiro-[pyrrolidine-3,3′-oxindole] **26** with imine **27** provided 2,5-disubstituted-3-spiro-pyrrolidine **28** in 47% yield, and thus it allowed for the first time the use of the annulation with a substituted spiro[cyclopropyl-1,3′-oxindole] such as **26** (Scheme 3).

Scheme 3. Synthesis of Spiro[cyclopropyl-1,3′-oxindole], **26**, and Successful Ring Expansion

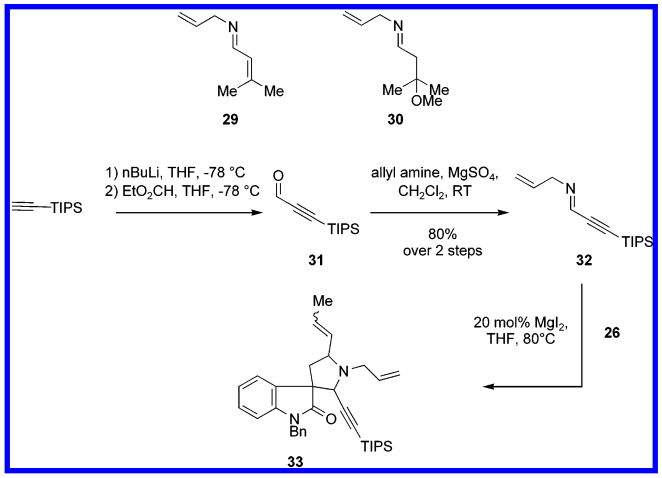


Having found a suitably substituted cyclopropane that successfully participates in the annulation reaction we sought to address the next critical task. An imine *N*-group had to be identified which would be susceptible to cleavage under mild conditions following formation of the spirofused pyrrolidine−oxindole. In this regard, it was not clear that an *N*-tosyl group could be removed under sufficiently mild conditions compatible with the anticipated functionality that would need to be present in the intermediates of the synthesis sequence en route to spirotryprostatin.

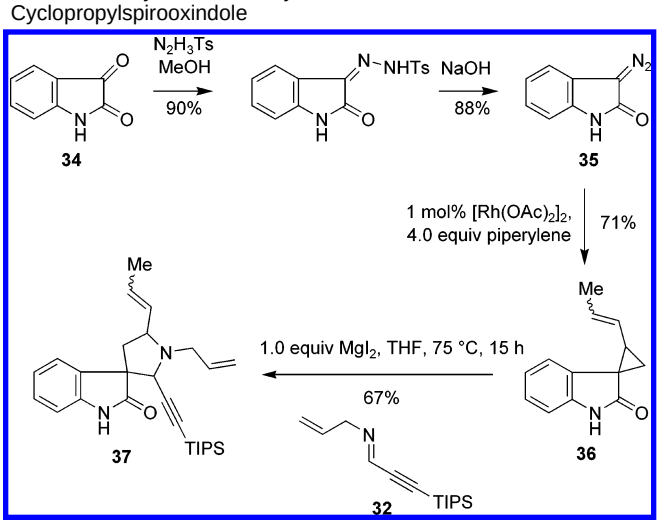
For a straightforward approach to spirotryprostatin B, the direct introduction of the prenyl moiety by ring expansion with prenal-derived allyl imine (**29**)[30] was desirable; alternatively, the cyclopropane-fragmentation/ring-expansion reaction with imine **30**[31] could also ultimately lead to a progenitor for the

(22) CCDC 199469 and CCDC 199470 contain the supplementary crystallographic data for **16** and **17** respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, U.K.; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
(23) Danishefsky, S.; Rovnyak, G. *J. Org. Chem.* **1975**, *40*, 114−115.
(24) Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4237−4244.
(25) For preparation of the cyclopropyl derivatives **19**−**23**, see Supporting Information.
(26) A simplification of the starting materials (R″ = H) requires the implementation of the C8−C9 olefin without the installation of a masked leaving group, a problem already solved in Danishefsky's synthesis of spirotryprostatin B (see ref 7).
(27) Danishefsky, S. *Acc. Chem. Res.* **1999**, *12*, 66−72.
(28) (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695−702. (b) Doyle, M. P.; Vanleusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787−789. (c) Padwa, A.; Austin, D. J.; Price, A. T.; Weingarten, D. M. *Tetrahedron* **1996**, *52*, 3247−3260. For recent reviews see: (d) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−939. (e) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. (f) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935.
(29) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H.; Buhro, W. E. *Tetrahedron Lett.* **1982**, *23*, 2261−2264. (These findings were confirmed by Davies: Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817−3824.) In the case of 2-substituted dienes, electronic factors associated with changes in the electrophilicities of the reactant metal carbenes proved relevant.
(30) VanMaanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; VanKoten, G. *Bull. Soc. Chim. Fr.* **1995**, *132*, 86−94.
(31) Imine **29** was obtained by condensation of allylamine with the known corresponding aldehyde: Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377−5387.

Scheme 4. Failure of the Ring-Expansion Reaction of Spiro[pyrrolidine-3,3′-oxindole], **26**, with Imines **29** and **30**, and Synthesis of Imine **33**



Scheme 5. Synthesis of Vinyl-Substituted Cyclopropylspirooxindole



prenyl moiety, related to one of William's intermediates.[6] However, the use of either imine **29** or **30** in the crucial key step did not provide any trace of the desired spiro-pyrrolidines (Scheme 4). Both imines were found to undergo self-condensation under the conditions of the annulation reaction (MgI_2 (10−20 mol %), THF, 80 °C, sealed tube).

We hypothesized that the use of a non-enolizable imine would preclude decomposition pathways that lead to undesired consumption of the starting material. Imine **33** was chosen, as the protected alkyne was expected to serve as a viable precursor for the prenyl side chain. The imine was accessed from triisopropylsilyl acetylene in two steps as shown in Scheme 4.[31,32] The TIPS-protected acetylene was converted to aldehyde **31** following metalation (*n*BuLi) and reaction with ethyl formate. Condensation with allylamine afforded imine **32** in 80% yield over two steps. The use of imine **32** in the ring-expansion reaction with **26** under standard conditions (20 mol % MgI_2, THF, 80 °C, sealed tube) led to the desired annulated product **33** in 56% yield as a mixture of diastereomers.

In the expansion reactions we have previously reported, *N*-benzyl-protected oxindoles have been employed exclusively as reacting partners. In the context of our synthesis endeavor, we became interested in addressing the question of whether the *N*-benzyl protecting group was at all necessary. Spiro[cyclopropyl-1,3′-oxindole] **36** was prepared from **34** in three steps via **35**, using a synthetic sequence similar to that described for the preparation of **25**. The reaction of **36** with imine **32** in the presence of one equivalent of MgI_2 gave spiro[pyrrolidine-3,3′-oxindole] **37**, demonstrating that protection of the indole nitrogen was not required in the ring-expansion step. The fact that the reaction, unlike in the case of *N*-protected spirooxindoles, necessitates the use of stoichiometric amounts of MgI_2 suggests that in these systems the Mg(II) forms a complex with the amide product and is precluded from being recycled and participating in multiple cycles of activation of the starting material. Under optimized conditions, **37** could be obtained in 67% yield as a mixture of diastereomers (Scheme 5). The compounds that constitute this mixture of stereoisomers differ only in the relative configuration at C-3, C-9, and C-8 as well as the double bond geometry. A subsequent series of investigations were aimed at establishing the structure of the diastereomers and ultimately completion of the synthesis.

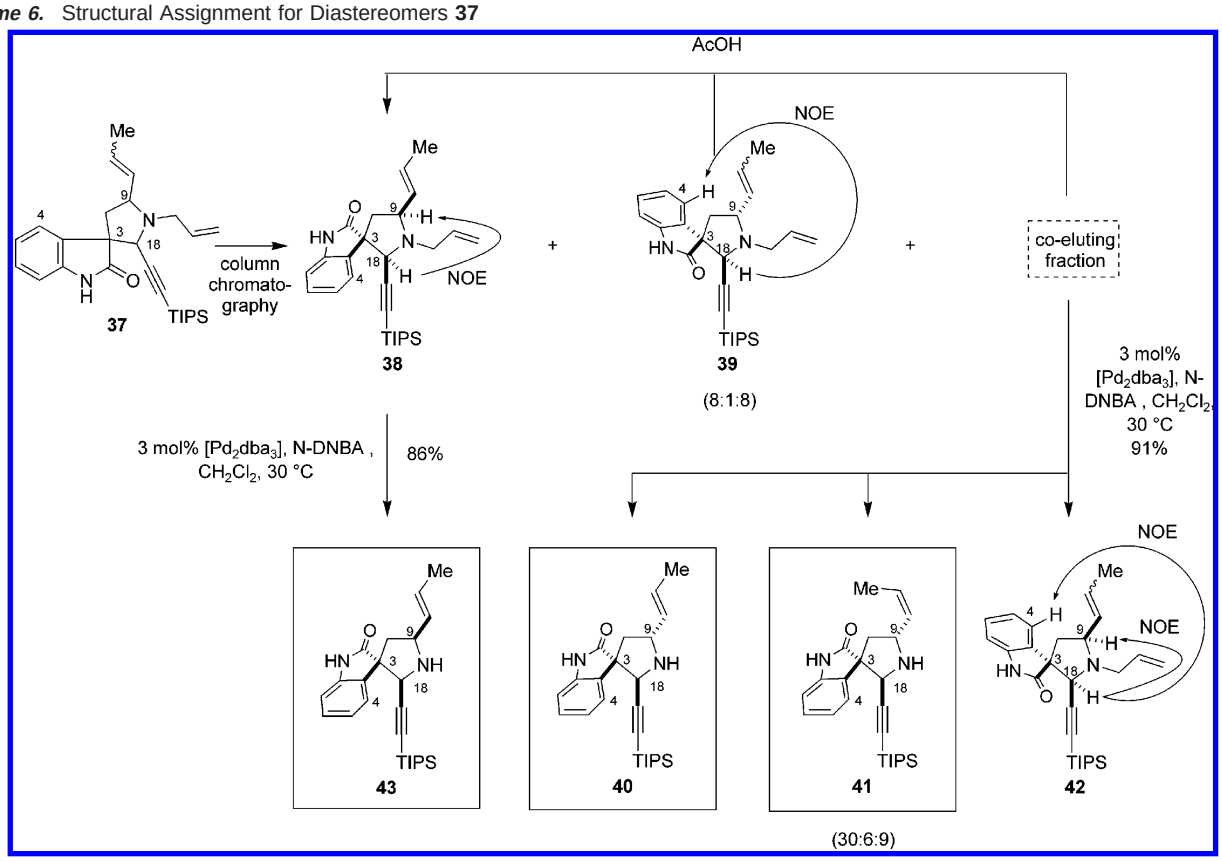
From the mixture of annulation products of the ring-expansion reaction, diastereomers **38** and **39** were obtained in pure form following chromatography on silica gel, together with a fraction of diastereoisomers in a ratio of 8:1:8 (**38**:**39**:others) that was not separated, with **38** as the major product of the annulation reaction. The two diastereomers **38** and **39** differ in the configuration at C-3 and C-9. The remaining mixture of diastereomers that could not be separated was subjected to Pd-catalyzed cleavage of the *N*-allyl protecting group (*N*-DNBA as allyl scavenger).[33,34] The products **40**−**42** of this high-yielding deprotection step were then separable by chromatography on silica gel and were obtained in a ratio of 30:6:9 (**40**:**41**:**42**). Similarly, **43** was obtained from **38** in 86% yield. Assignment of the relative configuration at C-3, C-18, and C-9 for compounds **38**-**42** was possible by analysis of the difference NOE spectra, with particular attention focused on the C-18, C-9, and C-4 protons. For compounds **38**, **40**, and **41**, irradiation of the proton at C-18 induced no enhancement of the proton at C-4, suggesting that these possessed the desired stereochemical relationship between C-18 and the spirocyclic quaternary center. For **39** and **42**, difference NOE enhancements were observed between C-18 and C-4 indicating that these compounds possess the undesired relative configuration between C-18 and the spirocyclic stereocenter. Irradiation of the proton at C-18 in **38** and **42** resulted in an NOE enhancement for the proton at C-9 indicating a *syn* relationship between these two protons. The absence of an enhancement for C-18 and C-9 indicated a 9,-18-*anti* relationship between the corresponding protons in **40** and **41**. This analysis led to the conclusion that the stereochemical outcome of the ring-expansion reaction of cyclopropylspirooxindole **36** with imine **33** was found to favor the formation of the products possessing the desired C-3,C-18-*syn* relationship in a ratio of 6:1. Additionally, we were pleased to observe that the stereoisomers resulting from the annulation reaction could be subjected to equilibration by treatment with

(32) (a) Journet, M.; Cai, D. W.; Di Michele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427−6428.

(33) $Pd(PPh_3)_4$ was prepared in situ from $[Pd_2dba_3]\cdot CHCl_3$ (6 mol % Pd) and PPh_3 (18 mol %) in CH_2Cl_2. Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253−266.

(34) Garro-Helion, F.; Merzouk, A.; Guibé, F. *J. Org. Chem.* **1993**, *58*, 6109−6113.

Scheme 6. Structural Assignment for Diastereomers **37**



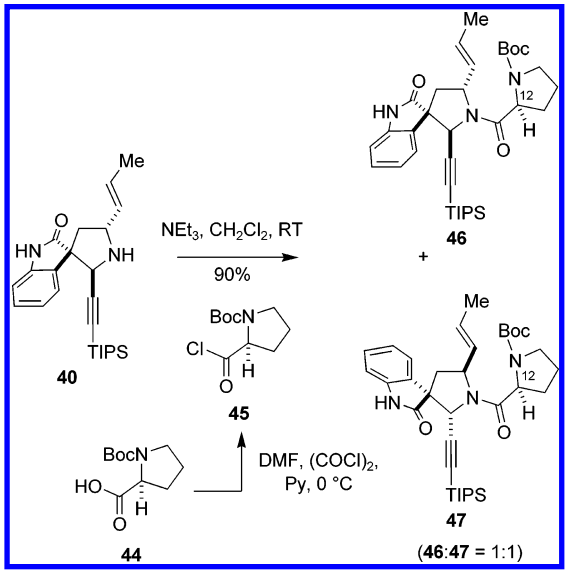
acetic acid under reflux for 16 h, resulting in 5:1 to 7:1 ratios in favor of **38** (Scheme 6).[35]

The assignment of the geometry of the olefin in **38**, **40**, and **41** was possible by analysis of the ^{1}H NMR chemical shift of the allylic proton at C-9, which resonates at lower field for *cis*-olefins as compared to *trans*-olefins.[36] Pyrrolidines **40** (δ 4.22 ppm) and **41** (δ 4.62 ppm) could be compared directly, because analysis of the observed NOE enhancements suggested that the relative stereochemical arrangement of the substituents on the pyrrolidine ring was identical. For compound **38**, no direct comparison was possible, but a *trans* geometry is proposed because the C-9 proton signal was found at very high field (δ 3.41 ppm). It is worth noting that the stereocenter at C-9 is not of crucial importance, as it is absent in the target end structure. Given the favorable results with respect to the diastereochemical outcome of the reaction, the synthesis of spirotryprostatin B could now be envisaged. Toward that end, we planned to carry the various suitable intermediates **40**, **41**, and **43** through the synthesis of spirotryprostatin B.

Synthesis of Spirotryprostatin B from 40

In the ensuing synthetic sequence, coupling of **40** and *N*-Boc-L-proline (**44**) was anticipated to lead to separation of diastereomeric coupled products **46** and **47**. Optimal results were obtained when **40** was treated with the acid chloride derived from *N*-Boc-L-proline (**45**).[37] Acid chloride **45** was prepared in situ from *N*-Boc-L-proline (**44**) with Vilsmeier−Haack reagent in the presence of pyridine.[38] The products **46** and **47** were obtained as a 1:1 mixture and could be readily separated by column chromatography on silica gel leading to enantiomerically pure **46** in 45% yield (Scheme 7).

Scheme 7. Resolution of **40**



Despite extensive ^{1}H NMR experiments, it was not possible to correlate the configuration at the C-12 stereogenic center to the stereogenic centers of the spiro-pyrrolidine-oxindole core

(35) Isomerization of the spirocenter of oxindoles is widely known and is proposed to occur via a retro-Mannich reaction see: (a) Wenkert, E.; Udelhofen, J. H.; Bhattacharyya, N. K. *J. Am. Chem. Soc.* **1959**, *81*, 3763−3768. (b) Seaton, J. C.; Nair, M. D.; Edwards, O. E.; Marion, L. *Can. J. Chem.* **1960**, *38*, 1035−1042. (c) Laus, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 315−317. (d) Yeoh, G. B.; Chan, K. C.; Morsingh, F. *Rev. Pure and Appl. Chem.* **1967**, 49−66.

(36) Martin, G. J.; Martin, M. L.; Lefèvre, F.; Naulet, N. *Org. Magn. Reson.* **1972**, *4*, 121−129.

(37) Buschmann, H.; Scharf, H. D. *Synthesis* **1988**, 827−830.

(38) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675−1681.

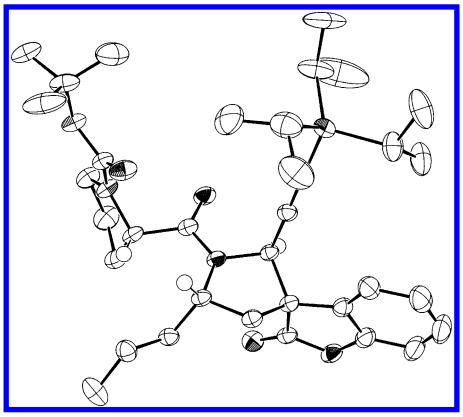


Figure 2. ORTEP drawing of **46**.[39]

for **46** and **47**. Fortunately, suitable crystals for X-ray crystallographic analysis were obtained from **46**, allowing for assignment of structure **46** and, therefore, of **47** as well (Figure 2).[39]

Oxidative cleavage of the olefin in **46** followed by further elaboration was planned, leading to the C-9 carboxylate required for subsequent installation of the diketopiperazine. When **46** was submitted to standard dihydroxylation conditions (OsO_4 (4 mol%), NMO·H_2O), diol **48** was obtained.[40] Cleavage of diol **48** by treatment with $Pb(OAc)_4$ was carried out without its prior purification and cleanly afforded aldehyde **49** in 97% yield over two steps.[41] Subsequent oxidation of aldehyde **49** to the corresponding acid **50** following Lindgren's procedure[42,43] and conversion to the methyl ester with diazomethane afforded **51**.[44] Removal of the TIPS-protecting group was accomplished in quantitative yield with TBAF in THF and gave **52**.[45] For the large-scale conversion of **46** into **52,** it is noteworthy that all five preceding steps can be carried out without purification of any of the various intermediates (**48**−**51**) in 80% overall yield (Scheme 8).

At this stage of the synthesis, conversion of the alkyne into the prenyl side chain was addressed. The success of this transformation would provide the opportunity for the required subsequent introduction of the endocyclic olefin and closure of the diketopiperazine to yield spirotryprostatin B. Theoretically, conversion of the C-19 alkyne into the corresponding aldehyde by alkyne semi-hydrogenation followed by oxidative olefin cleavage would set the stage for introduction of the appropriate prenyl side chain. However, as shown in Danishefsky's elegant study en route to spirotryprostatin A, an aldehyde closely related to **55** proved recalcitrant to a variety of olefination procedures.[4] Nevertheless, we decided to pursue further a plan involving the use of an olefination reaction for the introduction of the prenyl side chain, prompted by the fact that such a pathway would allow for facile access to spirotryprostatin B and, significantly, side-chain analogues of this natural product from aldehyde **55**.

Toward this end, hydrogenation of **52** catalyzed by Pd/$BaSO_4$ poisoned with quinoline yielded olefin **53** in 90% yield (Scheme 9).[46] The transformation of **53** to diol **54** was achieved with OsO_4/NMO·H_2O in THF/*t*BuOH/H_2O. The long reaction time (3 days) for this cleavage suggested that access to the C-19 olefin in **54** is rather limited, an observation that is consistent with the associated difficulties with olefination processes extensively examined by Danishefsky. Analysis by ^{1}H NMR spectroscopy revealed that diol **54** was formed as a single diastereomer. Interestingly, although the ^{1}H NMR spectra of all earlier intermediates were complicated by the presence of multiple rotamers due to restricted amide rotation for the Boc group, analysis of the spectra for **54** was simplified, as sharp resonances were uniformly observed (Scheme 9). From **54**, aldehyde **55** was obtained following glycol cleavage with $Pb(OAc)_4$.[41] Aldehyde **55** proved remarkably stable, no doubt likely as a result of the sterically hindered environment where it resides, allowing us focus on the critical olefination step.

Among the available procedures for the olefination of sterically hindered systems, the Wittig reaction is a commonly used transformation.[47] A variety of conditions was examined by employing the corresponding phosphonium salt (*n*BuLi, THF, RT; NaH/DMSO, DMSO, RT; KH/DMSO, Tol, 60 °C) none of which led to the desired product **59** (Scheme 10).[48] Traces of olefination product could be observed, but under all conditions examined, extensive epimerization at C-18 was observed to take place, and starting material **55** underwent decomposition. Addition of *i*PrMgCl to aldehyde **55**, followed by dehydration of the resulting alcohol, was investigated. Careful control of the amount of Grignard reagent led to conversion of **55** into alcohol **56** without epimerization at C-18 in 97% yield.[49] Various conditions for the direct dehydration of **56** were examined (Martin sulfurane (2−5 equiv), CH_2Cl_2, −20 °C to RT; $POCl_3$ (2 equiv), Py/CH_2Cl_2), but none provided the desired product **58**.[50,51] The use of a two-step procedure by formation of triflate **56** or tosylate **57** followed by elimination also failed due to the reluctance of **56** to form the corresponding triflate or tosylate (Scheme 10).[52]

We next turned our attention to the Julia−Lythgoe olefination reaction, as this three-step sequence has proved to be a valuable

(39) CCDC 196803 contains the supplementary crystallographic data for **46**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, U.K.; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(40) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973−1976.

(41) Rubottom, G. M. *Oxidation in Organic Chemistry*; Academic Press: New York, 1982.

(42) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890.

(43) An interesting alternative to obtain **50** directly from **46** through OsO_4-promoted catalytic oxidative cleavage was tested, but only traces of the desired material was obtained, making this direct method incompatible with the traditional three-step sequence. Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825.

(44) CH_2N_2 was prepared from *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine and was used as an ethereal solution. Fales, H. M.; Jaouni, T. M.; Babashak, J. F. *Anal. Chem.* **1973**, *45*, 2302−2303.

(45) Pattenden, G.; Robertson, G. M. *Tetrahedron Lett.* **1986**, *27*, 399−402.

(46) (a) Rosenmund, K. W. *Chem. Ber.* **1918**, *51*, 585−593. (b) Rao, A. V. R.; Reddy, S. P.; Reddy, E. R. *J. Org. Chem.* **1986**, *51*, 4158−4159. In this reference, Pd/$BaSO_4$ is misleadingly called Lindlar's catalyst (Pd/$CaCO_3$/PbO) in the experimental part. (c) Initial trials were undertaken using Lindlar's catalyst; however, only recovered starting material **52** was isolated under standard conditions. Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446−456.

(47) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318−1330.

(48) (a) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757−4766. (b) Oppolzer, W.; Wylie, R. D. *Helv. Chim. Acta* **1980**, *63*, 1198−1203.

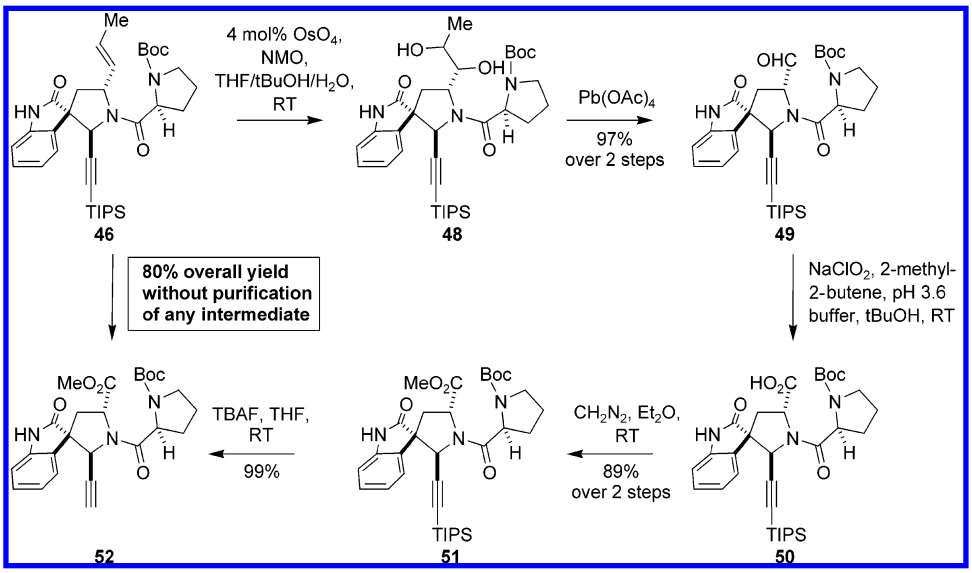
(49) Williams, L.; Zhang, Z. D.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673−11694. Corrigendum: Williams, L.; Zhang, Z. D.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1997**, *53*, 1923−1923.

(50) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2339−2342. (b) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327−4329. (c) Dolle, R. E.; Schmidt, S. J.; Erhard, K. F.; Kruse, L. I. *J. Am. Chem. Soc.* **1989**, *111*, 278−284.

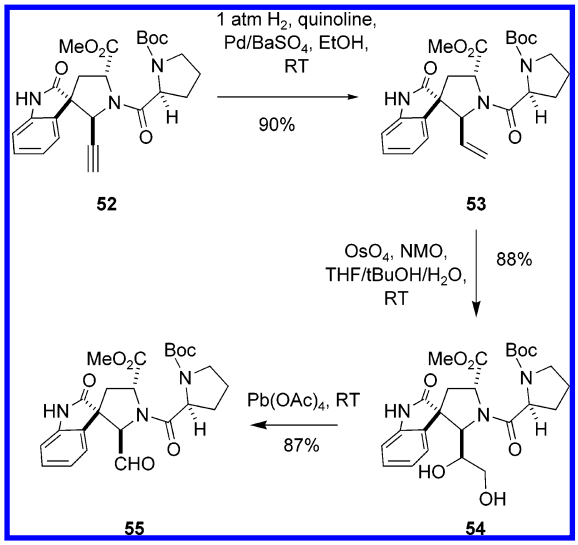
(51) (a) Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V. *J. Am. Chem. Soc.* **1986**, *108*, 3443−3452. (b) Shizuri, Y.; Yamaguchi, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 57−60.

(52) (a) Lefèbre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 1941−1946. (b) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967.

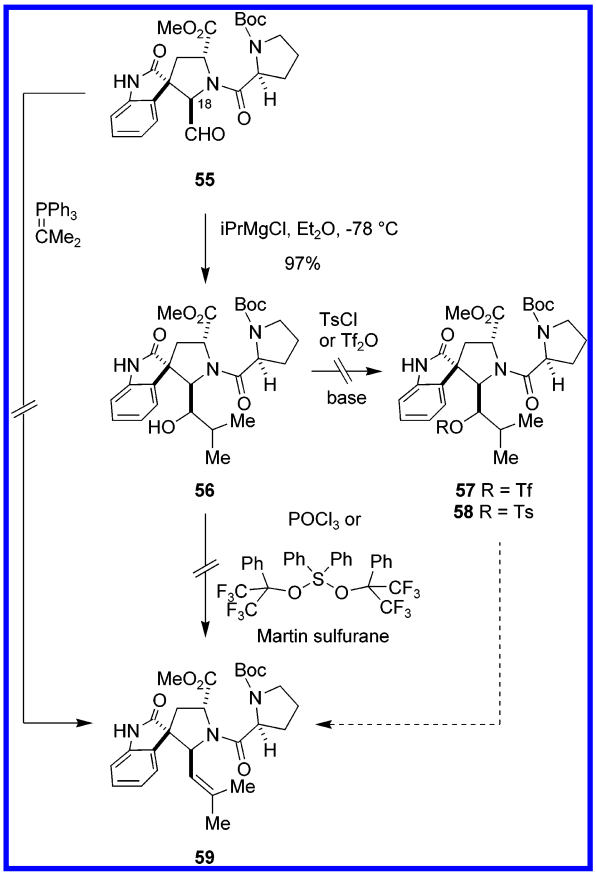
Scheme 8. Conversion of **46** into Advanced Intermediate **52**



Scheme 9. Conversion of **52** into Advanced Intermediate **55**



Scheme 10. Structural Correlation Studies



method for the generation of highly substituted olefins (Scheme 11).[53] Sulfone **61** was prepared by a liquid−liquid phase-transfer process from sodium benzene sulfinate (*i*PrI, Bu_4NI, H_2O/acetone/benzene) (**60**).[54] The Julia−Lythgoe sequence commenced with the addition of lithiated **61** to aldehyde **55** at −78 °C. Acylation of the hydroxyl in **62** afforded **63**, which was exposed to 2.5% Na/Hg in MeOH in the presence of Na_2HPO_4. From this set of reactions, olefin **64** was obtained in 11% overall yield from aldehyde **55**. Thus, olefination of aldehyde **55** proved possible; however, product **64** was found to have undergone extensive epimerization at C-18.[55]

The Julia−Kocieński modification of the one-pot olefination reaction developed by Julia was tested next.[56,57] The required sulfone **67** was available from **65** by alkylation under Mitsunobu conditions, followed by oxidation with Oxone (Scheme 12).[58] Treatment of aldehyde **55** with the lithium salt of sulfone **67** (obtained by treatment of **67** with LHMDS), afforded the desired product **59** without epimerization at C-18 in 78% yield. The structure of compound **59** was confirmed by X-ray crystallographic analysis (Figure 3).[59]

The Julia−Kocieński reaction is normally employed for efficient introduction of disubstituted olefins with selective

(53) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833−4836.
(54) Crandall, J. K.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327−1329.
(55) (a) McCombie, S. W.; Cox, B.; Ganguly, A. K. *Tetrahedron Lett.* **1991**, *32*, 2087−2090. (b) Gurjar, M. K.; Srinivas, N. R. *Tetrahedron Lett.* **1991**, *32*, 3409−3412.
(56) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178.
(57) Kocieński, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365−366.
(58) Ward, R. S.; Roberts, D. W.; Diaper, R. L. *Sulfur Lett.* **2000**, *23*, 139−144.

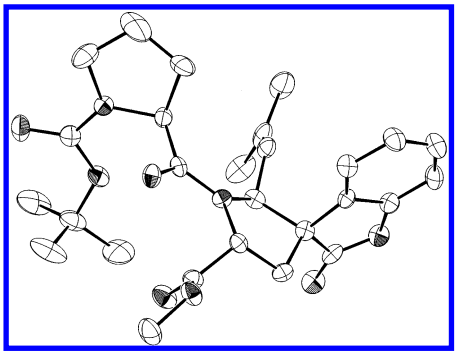
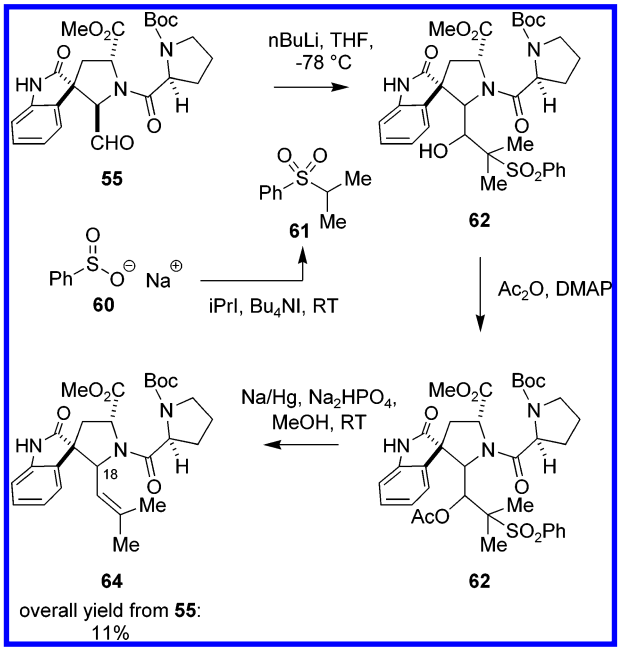
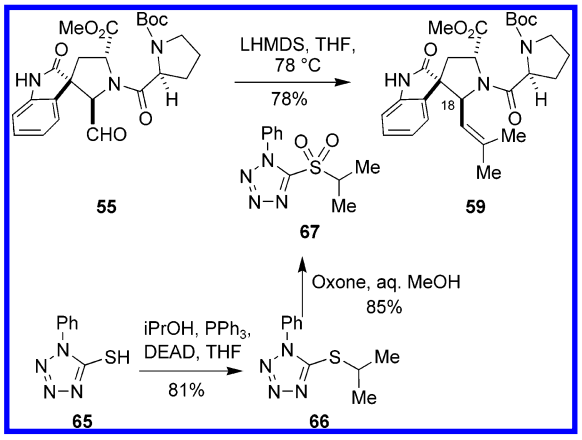


Figure 3. ORTEP drawing of **59**.

Scheme 11. Completion of the Synthesis from **55**

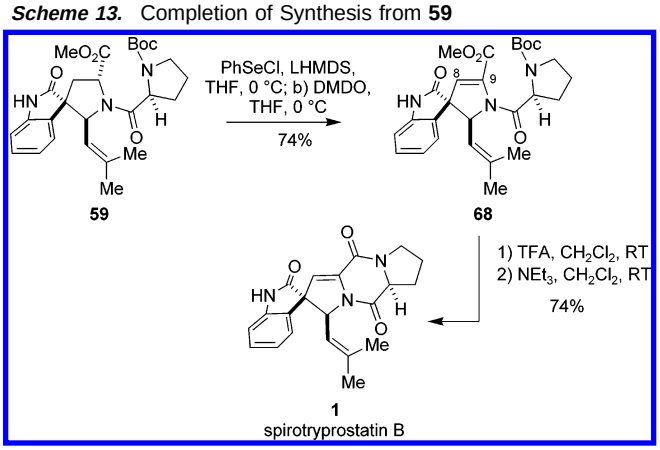


Scheme 12. Attachment of Side Chain onto **55**



formation of the *trans*-isomers. To the best of our knowledge, the use of this reaction for the formation of trisubstituted double bonds has not yet been the subject of investigations.[60] Consequently, although the Julia−Kocieński reactions with β-branched aryl sulfones (e.g. with 2-methyl-heptyl-aryl-sulfone) are known,[61] the use of α-branched aryl sulfones has not been reported.

Scheme 13. Completion of Synthesis from **59**



From **59**, the synthesis of spirotryprostatin B was completed in four steps, following the Danishefsky route (Scheme 13).[7] Thus, selenylation of **59** followed by oxidation/elimination with DMDO afforded **68** (74%).[62,63] Deprotection of the proline moiety and subsequent formation of the lactam leading to the diketopiperazine ring led to spirotryprostatin B (**1**) in 74% yield. The physical characteristics observed (^{1}H and ^{13}C NMR spectra, MS, IR, optical rotation) were found to be identical to those reported in the literature for natural material.

Synthesis of Spirotryprostatin B from Diastereomer 41

Intermediate **41** differs from **40** only in the geometry of the olefinic double bond. Thus, proceeding through the sequence of synthetic steps employed previously for synthesis of spirotryprostatin B from **40** would lead to a common advanced intermediate in the form of **49** (Scheme 14). Treatment of **41** with the acid chloride derived from *N*-Boc-L-proline (**45**) afforded a 1:1 mixture of chromatographically separable **69** and **70**. Because we were unable to obtain crystalline material from either of the two coupling products, structural assignment was therefore possible only after conversion of **69** to aldehyde **49**, which had been previously prepared. Coupling product **69** was converted into the corresponding aldehyde via diol **71** in 75% overall yield. The analytical characteristics observed for this aldehyde were found to be identical to those found previously for **49**. Therefore, structure **69** was assigned as shown in Scheme 14.

Synthesis of Spirotryprostatin B from 43

The difference between **40** and **43** concerns the relative configuration at the C-9 stereocenter. Because this stereocenter is absent in the natural product, use of the synthetic sequence used for the synthesis of spirotryprostatin B from **40** to **43** would result in formation of common intermediate **68**.

Coupling of **43** with the acid chloride derived from *N*-Boc-L-proline (**45**) afforded a mixture of products **72** and **73** which were inseparable by column chromatography. The mixture of products was submitted to the conditions for conversion of the

(59) CCDC 196804 contains the supplementary crystallographic data for **59** These data can be obtained free of charge via www.ccdc.cam.ac.uk/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, U.K.; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

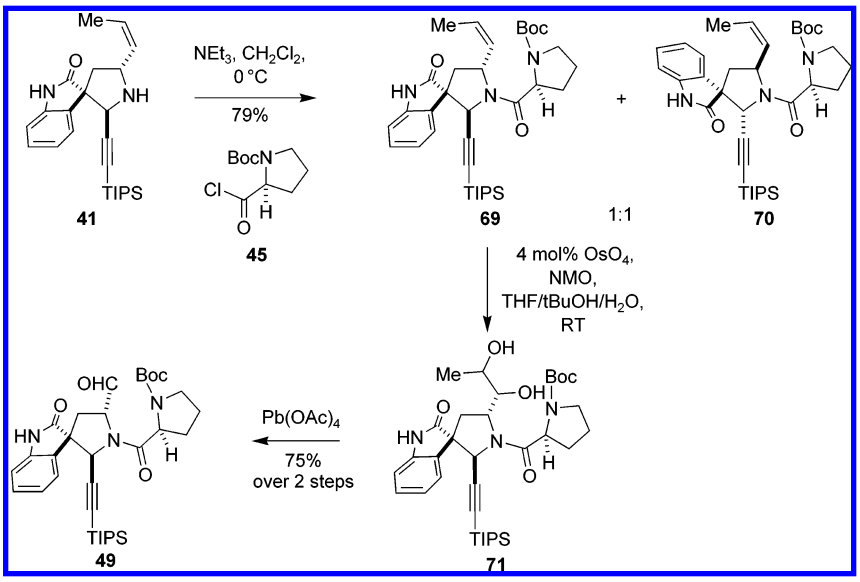
(60) Nirenburg, V. L.; Postovskii, I. Y. *Izv. Vyssh. Uchebn. Zaved. Khim. Tekhnol.* **1965**, *8*, 258.

(61) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26−28.

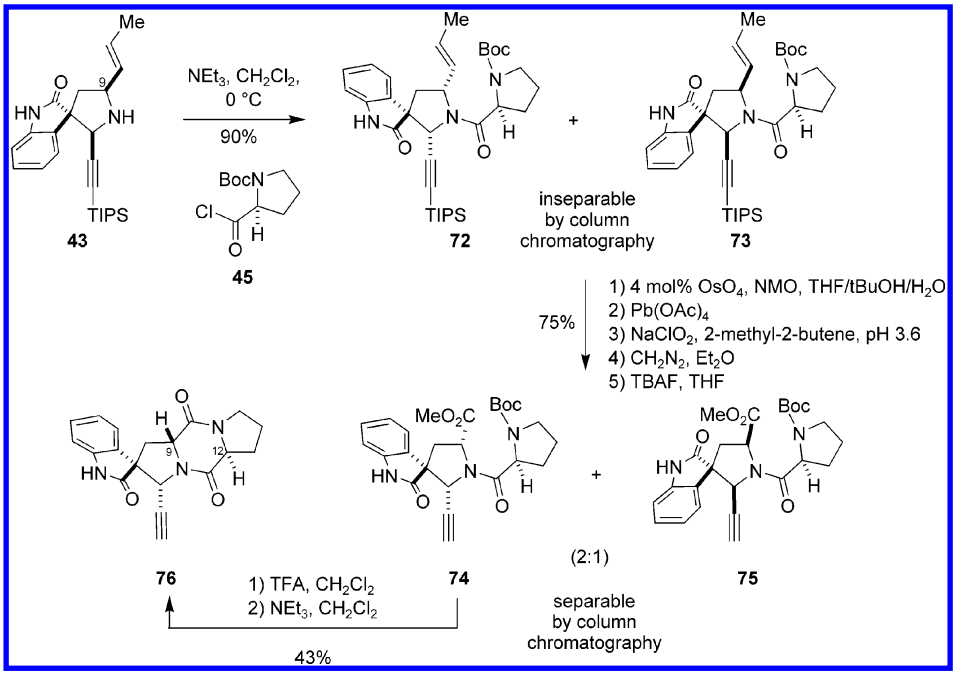
(62) Reich, H. J.; Reich, I. J.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815.

(63) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377−2377.

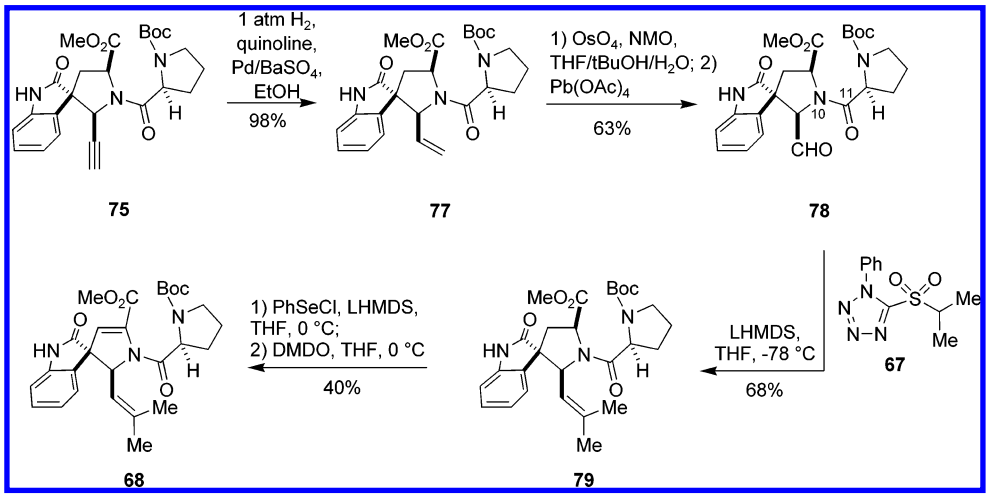
Scheme 14. Synthetic Elaboration of **41**



Scheme 15. Elaboration of **43**



Scheme 16. Conversion of **75** into Advanced Intermediate **68**



substituted vinyl group into the C-9 methyl ester followed by removal of the TIPS protecting group (vide infra). All of these steps were carried out without purification of the intermediates. Compounds **74** and **75** in a 2:1 ratio resulted from this sequence as isomers separable by chromatography on silica gel. The fact that the obtained ratio is not 1:1, as previously observed, may result from a (partial) kinetic resolution of **43** with **45**, but partial loss in the conversion of **73** to **75** cannot be ruled out. (Scheme 15).

Assignment of the configuration for **74** and **75** was not possible, as neither compound yielded suitable crystals. The major product **74** was treated with TFA followed by triethylamine to yield **76**. No NOE enhancements could be observed between the C-9 and C-12 protons, indicating that the *trans*-diketopiperazine has been produced from **74**. Although the absence of an NOE is not an absolute proof, spirotryprostatin A, a *cis*-diketopiperazine, showed a pronounced NOE for these protons (Scheme 16).[2] Assuming that the assignment of **74** is correct, we continued our synthetic route with compound **75**.

Following the same synthetic steps as in our earlier sequence, **75** was converted to aldehyde **78** via olefin **77**. In this sequence, as compared to the C-9 epimeric compounds, we observed spectroscopic evidence that indicated the occurrence of four rotamers, seemingly due to restricted rotation around the N-10−C-11 amide bond. The Julia−Kocieński reaction of aldehyde **78** to product **79** proceeded in 68% yield. From **79**, the implementation of the C8−C9 double bond proved that the assumption about the isomer assignment of **74** and **75** had indeed been correct, as the isolated compound was identical to **68** (Scheme 6), thus providing spirotryprostatin B from **43**.

Conclusions

We have described a synthesis route to spirotryprostatin B whose key step is the annulation reaction of cyclopropyl-spiro-oxindole. This transformation demonstrates the ability to carry out such annulation reactions with vinyl-substituted cyclopropanes and a synthetically versatile alkynyl imine. We have shown that the compound possessing the desired relative configuration can be isolated in good yields from a 6:1 mixture of diastereomers after deprotection and used to access the targeted natural product. In the course of structural elucidation studies of the various products formed, we have shown that a number of the other diastereomeric products can be employed to converge onto spirotryprostatin B. An additional salient feature of the route is the development of an olefination reaction for the installation of the hindered prenyl side chain. The methodological study demonstrates the feasibility of the Julia−Kocieński process in the preparation of hindered trisubstituted olefins. The synthesis along with our studies in other systems underscores the versatility of the annulation reaction of imines and cyclopropyl-spiro-oxindoles in providing access to a wide range of alkaloid products.

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Supporting Information Available: Experimental procedures and spectral data for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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