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Synthetic studies toward the spiroimine unit of the spirolides*

Stéphanie M. Guéret and Margaret A. Brimble‡

Department of Chemistry, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

Abstract: Synthetic studies toward the spiroimine unit of the spirolide family of shellfish biotoxins are described. Several strategies for introduction of the C7, C29, and C32 stereocenters of the A,E-ring system of the spirolides are described, such as spironitrone formation, Birch reductive alkylation, and asymmetric Diels–Alder cycloadditions.

Keywords: Birch reduction; metathesis; spiroimine; spirolides; spironitrone.

INTRODUCTION

Harmful algal blooms are an international health problem responsible for more than 60 000 intoxications per year with an overall mortality of approximately 1.5 % [1]. Owing to the possible adverse impact on the shellfish consumer, harmful algal blooms are monitored all over the world using various methods, thus leading to the discovery of new families of marine toxins. In 1995, spirolides A–D (**1–4**) were first isolated from the digestive glands of mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) from the east coast of Nova Scotia in Canada [2]. To date, 14 members (**1–14**) of the spirolide family have been isolated world-wide (Fig. 1) [3]. These marine biotoxins are metabolites of the dinoflagellates *Alexandrium ostenfeldii* and *A. peruvianum*.

The spirolides exhibit remarkable biological activity. They are considered as fast-acting neurotoxins owing to their potent effect in the mouse bioassay [4]. They are also weak activators of L-type calcium channels [2] which renders these compounds attractive candidates for the treatment of cardiovascular disorders. Recently, the first X-ray structure of 13-desmethyl spirolide C (**6**) bound to the nicotinic acetylcholine binding protein was obtained, showing that both the cyclic imine and the *bis*-spiroacetal moieties are involved in key protein binding interactions [5]. 13-Desmethylspirolide C (**6**) is the most potent general nonpeptidic nicotinic acetylcholine antagonist reported to date.

The relative stereochemistry of the spirolides has been tentatively established using a combination of molecular modeling and NMR studies [6–8], and bears a close resemblance to the absolute stereochemistry established for pinnatoxin A [9]. The spirolides contain a spiroacetal or *bis*-spiroacetal unit together with a rare 7,6-spirocyclic imine. To date, the total synthesis of the spirolides remains an unmet synthetic challenge. The synthesis of the 5,5,6-*bis*-spiroacetal moiety of spirolides B (**2**) and D (**4**) has been reported by the Ishihara [10] and Brimble [11] research groups. However, the spiroimine unit of the spirolides has not yet been synthesized. For several years, our research group has focused on the development of synthetic pathways to access this unusual 7,6-spiroimine unit. This paper summarizes

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‡Corresponding author

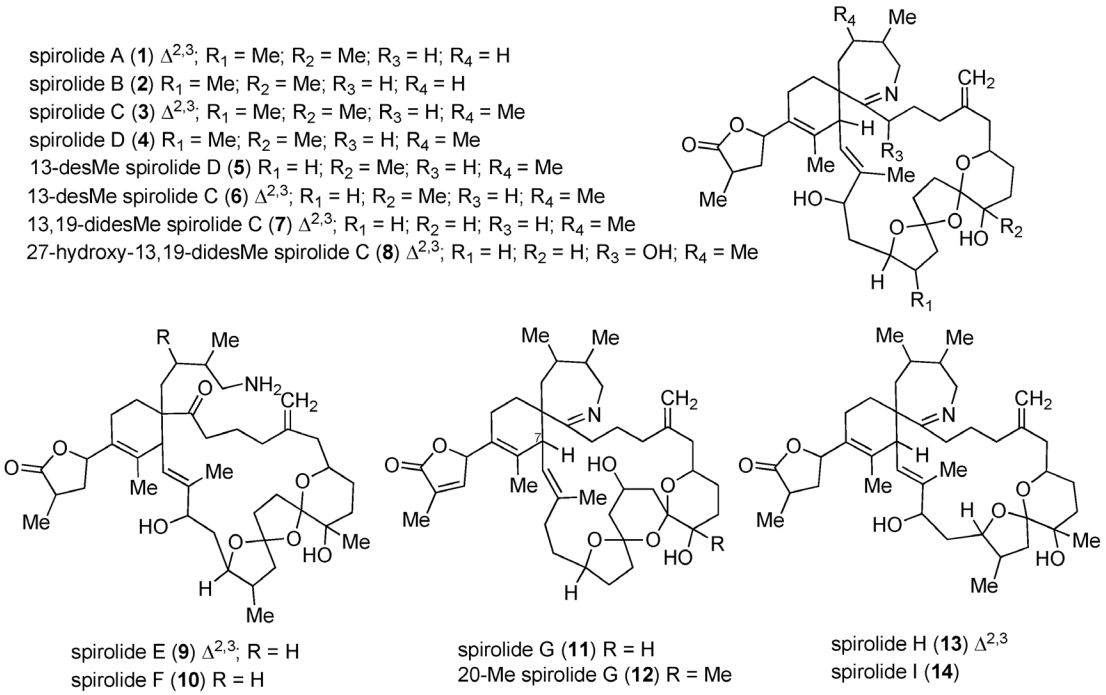
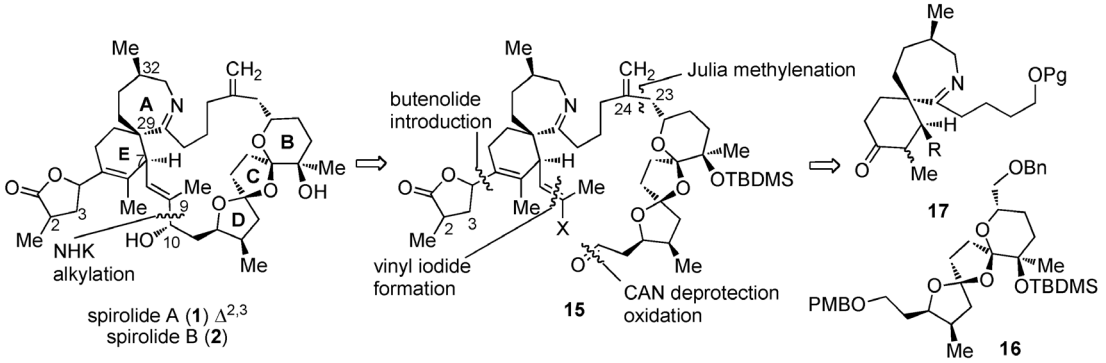


Fig. 1 The 14 members of the spirolide family of marine biotoxins.

our various attempts to access this 7,6-spiroimine with our efforts, culminating in the enantiopure synthesis of an advanced analogue of the spiroimine unit of the spirolides.

The first key disconnection in our proposed retrosynthesis of spirolides A (**1**) and B (**2**) (Scheme 1) involves an intramolecular asymmetric Ni^{II}/Cr^{II}-mediated Nozaki–Hiyama–Kishi (NHK) coupling [12,13] between an aldehyde and a vinyl halide to form the C9–C10 bond of the macrocyclic ring. This strategy was successfully used by Kishi et al. for the synthesis of pinnatoxin A [9] and pteriatoxins [14] and also by Romo and co-workers in the total synthesis of gymnodimine [15]. The resulting aldehyde **15** is obtained by deprotection of the *p*-methoxybenzyl protecting group using CAN followed by oxidation. The butenolide functionality at the C5 position of the 6-membered E ring is introduced late in the synthesis via diastereoselective vinylogous Mukaiyama aldol addition of a silyl-

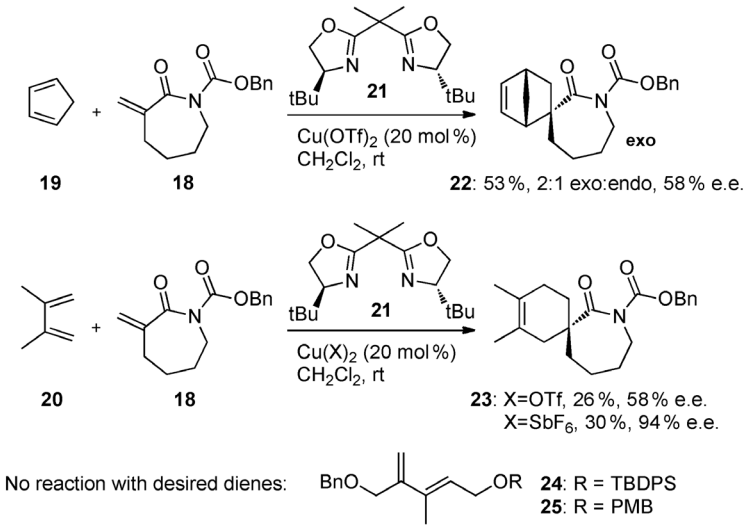


Scheme 1 Retrosynthetic analysis of spirolides A and B.

oxyfuran to a ketone in the 6-membered ring of the spirolides as reported by Kong and Romo [16]. The second key disconnection uses a Julia methylenation [17–19] in order to couple the *bis*-spiroacetal **16** and the advanced spiroimine **17** forming the C23–C24 bond of the spirolides. The resulting spiroimine moiety **17** of the spirolides possesses three stereocenters; a C29 quaternary stereocenter linked to both the 6- and 7-membered rings and assigned to have the *S** relative stereochemistry, a 7*S** stereocenter α to the quaternary center exhibiting an *anti* relationship to the imine functionality on the A ring and a methyl group at C32 with an *R** configuration.

PRELIMINARY STUDIES

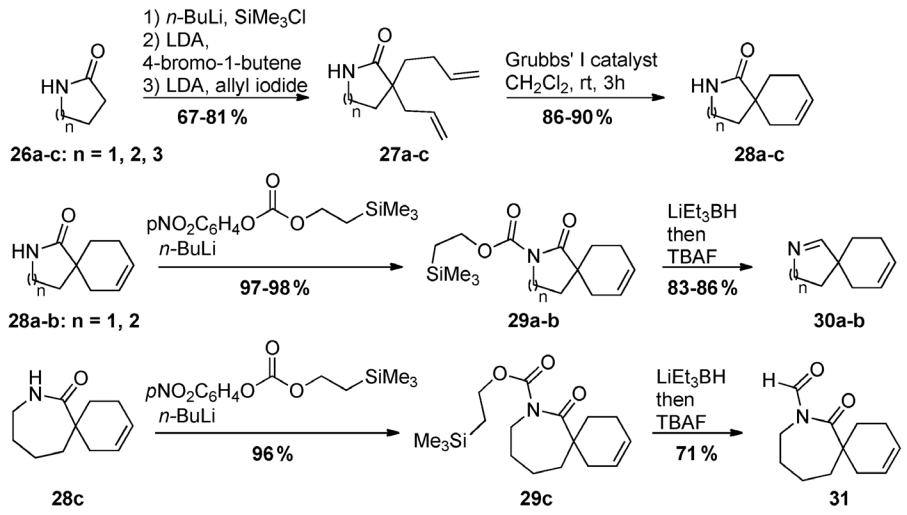
Our initial approach investigated the formation of bicyclic spirolactams via Diels–Alder cycloaddition of α-methylenelactam **18** with cyclopentadiene **19** or 2,3-dimethyl-1,3-butadiene **20** in the presence of the copper complex of (*S*,*S*)-*t*-BuBOX **21** [20]. The desired cycloadducts **22** and **23** were obtained with *exo*-selectivity, in moderate yield. However, when more complex dienes **24–25** were subjected to the same Diels–Alder conditions, none of the desired adducts were observed (Scheme 2).



Scheme 2

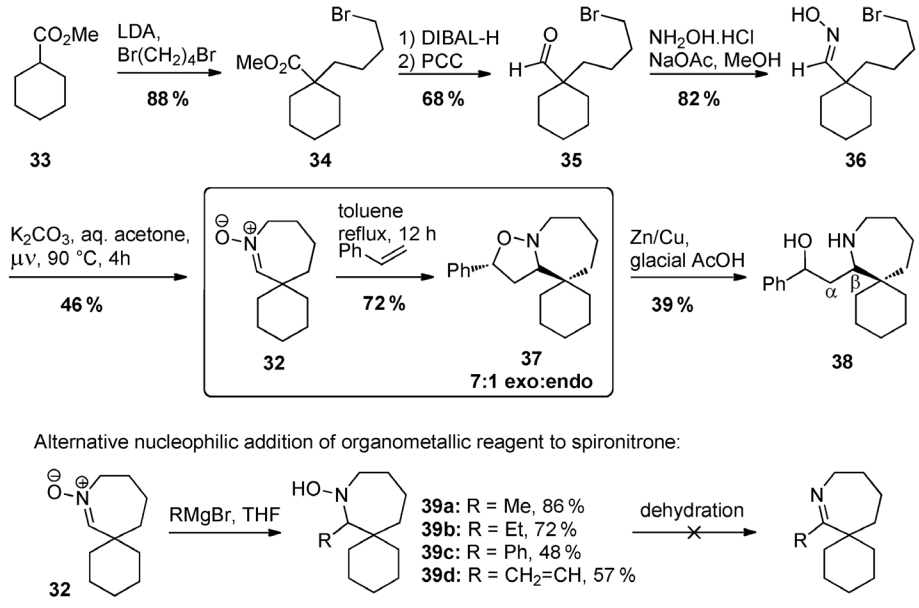
A second approach was next investigated using a double-alkylation/ring-closing metathesis strategy to prepare spirolactams as precursors to spiroimines (Scheme 3) [21,22]. Lactams **26a–c** of varying ring size were first *N*-TMS protected then subjected to double α-alkylation using lithium diisopropylamide (LDA) and alkyl halide in good overall yield. The key ring-closing metathesis proceeded in excellent yield by treatment of dienes **27a–c** with Grubbs' type 1 catalyst. Reduction of the five- and 6-membered lactams **28a,b** in three steps was successful: protection with a TEOC group, reduction of the amide carbonyl group of compound **29a,b** using lithium triethylborohydride and final exposure to tetrabutylammonium fluoride (TBAF) afforded desired 5,5- and 5,6-spirocyclic imines **30a,b** in good yield.

However, for the 7-membered spirolactam **28c** an alternative reduction took place leading to the formation of *N*-formyl spirolactam **31** (Scheme 3). This result can be rationalized by the considerable steric hindrance of the lactam carbonyl group forcing the hydride to attack the more accessible carbonyl group of the carbamate protecting group.



Scheme 3

A few years later, we reported a novel approach in which a model 6,7-spironitrone was synthesized as a precursor to the spiroimine moiety of the spirolides (Scheme 4) [23]. The key spironitrone was obtained in five steps via mono-alkylation of methyl cyclohexanecarboxylate **33**, reduction of ester **34**, and reaction of the resulting aldehyde **35** with hydroxylamine chloride to give bromo-oxime **36** that finally underwent cyclization using potassium carbonate in acetone-water in a microwave reactor. Unstable spironitrone **32** was immediately used in a 1,3-dipolar cycloaddition with an electron-rich dipolarophile, styrene, affording the desired cycloadduct **37** in good yield with an *exo*:*endo* ratio of 7:1. Reductive cleavage of the N–O bond of isoxazolidine using a zinc–copper couple in acetic acid proceeded in low yield to give the β-amino alcohol **38**. Nucleophilic addition of commercially avail-

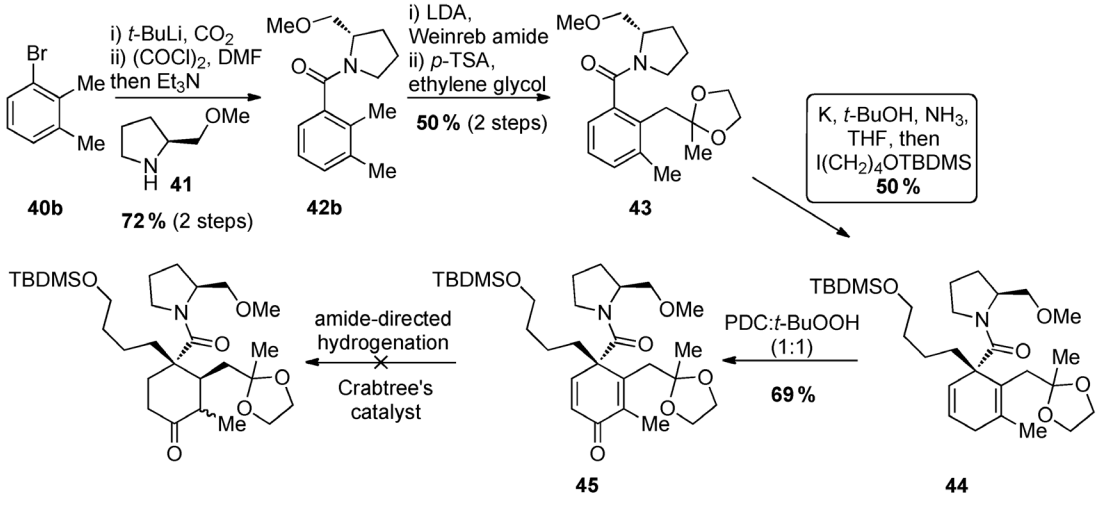


Scheme 4

able Grignard reagents to spironitrone **32** afforded a range of hydroxylamines **39a–d**, in variable yields. Unfortunately, hydroxylamines **39a–d** could not be dehydrated to the desired spiroimines (Scheme 4).

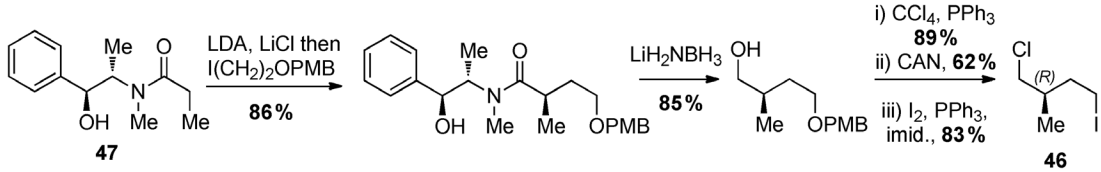
BIRCH REDUCTIVE ALKYLATION: ACCESS TO ENANTIOPURE SPIROLACTAMS

The three studies described above were unable to deliver the desired spiroimine ring system even in racemic form. Given this background, we decided to investigate a novel model system making use of a highly diastereoselective Birch reductive alkylation to introduce the C29 stereocenter of the spirolides in enantiopure form. Aryl bromide **40** was reacted with chiral auxiliary **41** to give chiral benzamide **42b**. A protected methyl ketone side chain was successfully incorporated α to the amide via *ortho*-metallation leading to advanced benzamide **43**. It was envisaged that this acetal could be converted to a vinyl halide, thus providing a handle to later couple the spiroimine unit with the *bis*-spiroacetal moiety of the spirolides. Alkylation of benzamide **43** under optimized Birch reductive alkylation conditions with 1-*t*-butyldimethylsilyloxy-4-iodobutane afforded alkylated product **44** in 50 % yield with complete regioselectivity. Cyclohexadiene **44** was reacted with PDC/*t*-BuOOH to give cyclohexadienone **45**. Unfortunately, amide-directed hydrogenation was unsuccessful using the complex substrate **45** and also using simpler analogues, thus preventing introduction of the required *anti* relationship between the chiral amide attached to the quaternary center and the neighboring protected methyl ketone (Scheme 5).



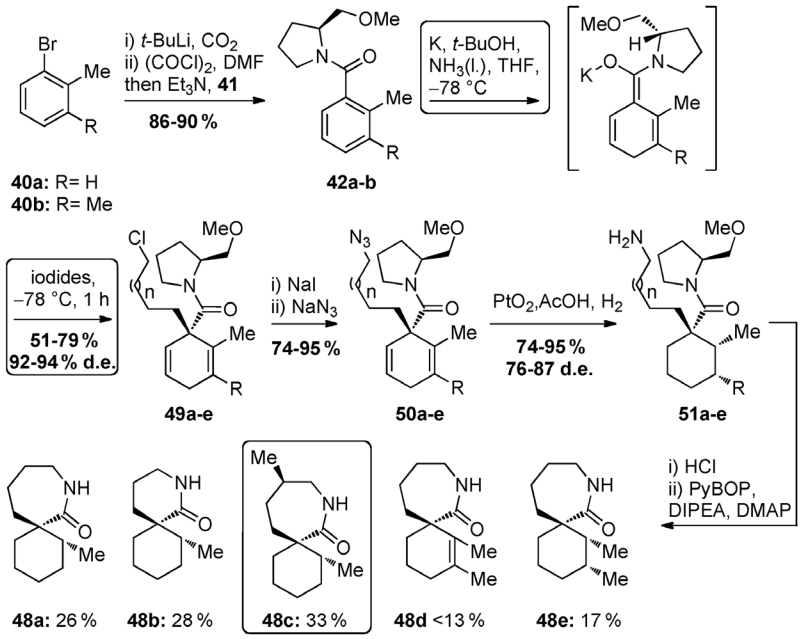
Scheme 5

On a positive note, during this study chiral iodide **46** was successfully prepared in five steps from (*S*,*S*)-pseudoephedrine propionamide **47** using a diastereoselective Myers' alkylation, providing the first reported access to the C32 stereocenter of the spirolides A and B (Scheme 6).



Scheme 6

Although this Birch reductive alkylation strategy could not be applied to the synthesis of the spiroimine unit of the spirolides, this study did provide a powerful convergent method to prepare a range of enantiopure bicyclic α,α-disubstituted spirolactams **48a–e** (Scheme 7) [24].

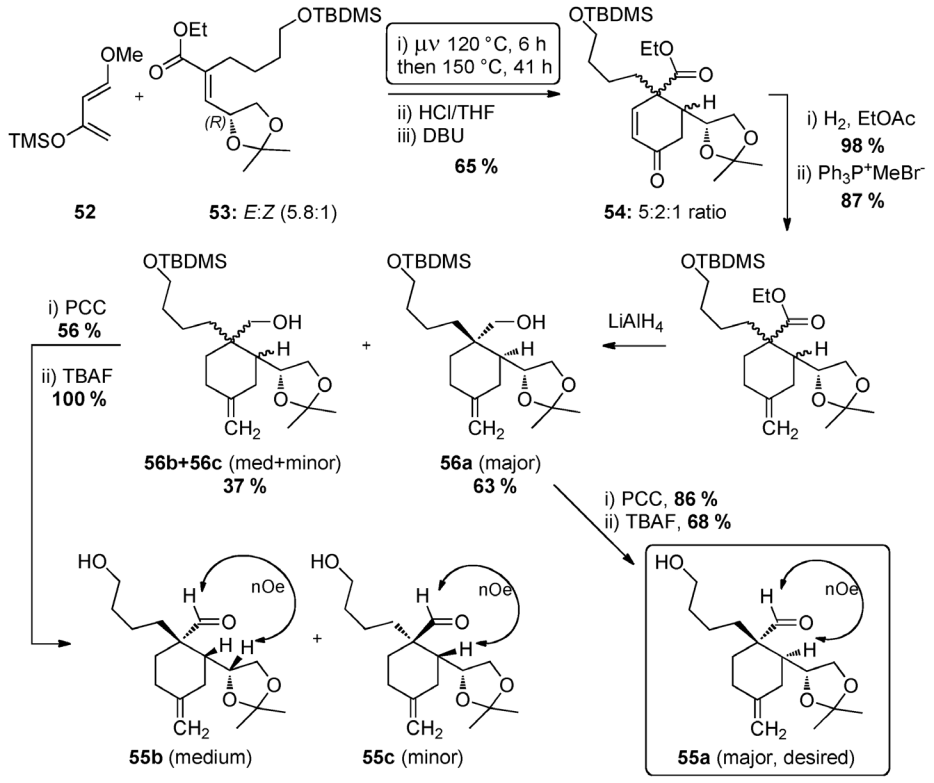


Scheme 7

The spirolactams were obtained in five steps from monomethyl and dimethyl chiral benzamides **42a,b** using a highly diastereoselective Birch reductive alkylation with various electrophiles to give cyclohexadienes **49a–e** followed by stereoselective heterogeneous hydrogenation of azides **50a–e** that proceeded *anti* to the amide functionality [25] and ultimately intramolecular cyclization of the resulting amines **51a–e** formed the lactam ring. Importantly, selective introduction of an additional methyl group in spirolactam **48c** provides the core 7,6-A,E ring system of the spirolides A (**1**) and B (**2**).

DIELS–ALDER STRATEGY: ACCESS TO AN ENANTIOPURE SPIROIMINE

Our most recent approach to the spiroimine unit (A,E rings) of the spirolides A and B focused on the use of a stereoselective Diels–Alder cycloaddition in order to simultaneously establish both the C7 and C29 stereocenters [26]. The key Diels–Alder reaction between Danishefsky's diene **52** and an advanced enantiopure (*R*)-dienophile **53** (*E*/*Z* 5.8:1 ratio), obtained from the Horner–Wadsworth–Emmons condensation of (*S*)-glyceraldehyde acetonide with a mono-alkylated phosphonate, gave cycloadduct **54** in 65 % yield as an inseparable mixture of three diastereoisomers in a 5:2:1 ratio, after 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) elimination. Further transformation of cyclohexenone **52** over five steps to aldehyde-alcohol **55a–c** enabled the separation of each diastereoisomer (Scheme 8). Extensive nuclear Overhauser effect (nOe) studies and further conversion of minor diastereoisomer **55c** to an unprecedented crystalline 14-membered di-aldimine [27] confirmed the absolute stereochemistry of the major diastereoisomer **55a** obtained from the Diels–Alder reaction to be that required for the C7 and C29 stereocenters of the spirolides A and B. The unequivocal assignment of the stereochemistry for the

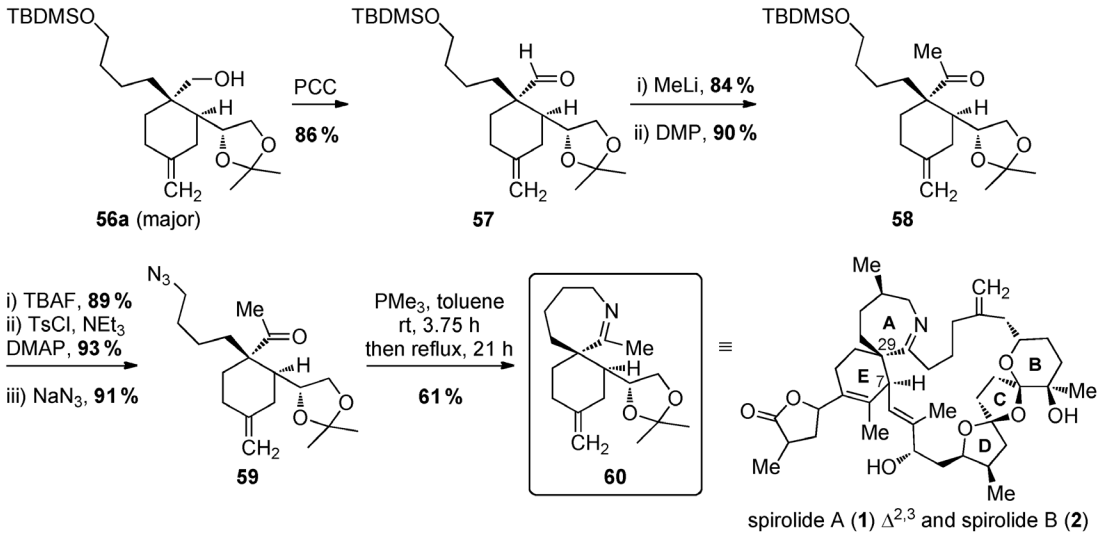


Scheme 8

major distereoisomer also established that this diastereoisomer results from approach of Danishefsky's diene on the less hindered top face of the *E*-dienophile.

Alcohol **56a** was then oxidized using pyridinium chlorochromate (PCC) followed by alkylation of the resulting aldehyde **57** using methyl lithium to afford advanced methyl ketone **58** after Dess–Martin periodinane oxidation. The key keto-azide **59** was easily obtained in three steps via TBAF deprotection, tosylation, and azide formation. The second highlight of this study was the successful synthesis of the optically pure 7,6-bicyclic ketimine **60** in 61 % yield via intramolecular aza-Wittig cyclization using trimethylphosphine (Scheme 9).

This successful efficient synthetic route to 7,6-spiroimine **60** containing both the C7 and C29 stereocenters of the spirolides represents an important milestone in progress toward the spiroimine unit of the spirolides and provides a convergent and viable pathway to complete the total synthesis of the spirolides.



Scheme 9

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