ORGANIC LETTERS

2010
Vol. 12, No. 22
5226−5229

Synthesis of a Functionalized 7,6-Bicyclic Spiroimine Ring Fragment of the Spirolides

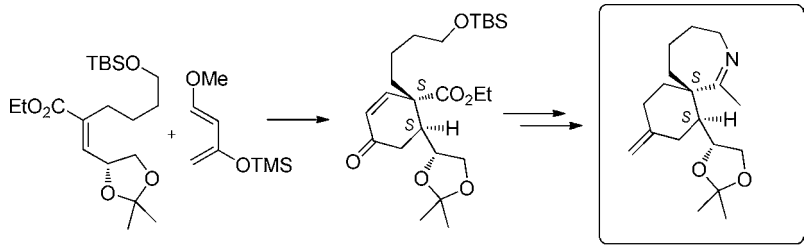
Stéphanie M. Guéret, Daniel P. Furkert, and Margaret A. Brimble*

Department of Chemistry, University of Auckland, Private Bag 92019, Auckland, New Zealand

m.brimble@auckland.ac.nz

Received September 20, 2010

ABSTRACT



The asymmetric synthesis of a functionalized 7,6-spiroimine related to the spirolides is described. Intermolecular Diels−Alder cycloaddition of a chiral trisubstituted dienophile and Danishefsky's diene enabled simultaneous installation of the C7 and C29 stereocenters. Further transformations and late-stage *aza*-Wittig cyclization afforded the spiroimine in good yield. During this study, an unprecedented 14-membered dialdimine was also obtained.

Spirolides A−D (**1**−**4**) were first isolated from the digestive glands of shellfish collected from the east coast of Nova Scotia in Canada.[1] These toxins are metabolites of the dinoflagellates *Alexandrium ostenfeldii* and *A. peruvianum*. To date, 14 members of this family have been identified from around the world.[2] The spirolides are considered as fast-acting neurotoxins and are activators of L-type calcium channels.[3] They also represent the most potent nonpeptidic nicotinic acetylcholine receptor antagonists as demonstrated by a recently obtained X-ray structure of 13-desmethyl spirolide C (**5**) bound to acetylcholine binding proteins (AChBP).[4]

The remarkable biological activity of the spirolides renders them attractive candidates for the development of lead compounds for treatment of cardiovascular and neurological diseases. However, total synthesis of these highly complex marine biotoxins has not yet been reported. The proposed relative stereochemistry[5,6] bears a close resemblance to that of pinnatoxin A[7] whose absolute stereochemistry is known. The structure of the spirolides can be divided into two parts (Figure 1): the bis-spiroacetal unit previously synthesized by the Ishihara[8] and Brimble[9] groups and the cyclic spiroimine moiety known to be essential for biological activity. Due to the presence of a seven-membered imine ring, a quaternary stereocenter at the ring junction and the

(1) Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159.

(2) Guéret, S. M.; Brimble, M. A. *Nat. Prod. Rep.* **2010**, *27*, 1350.

(3) Gill, S.; Murphy, M.; Clausen, J.; Richard, D.; Quilliam, M.; MacKinnon, S.; LaBlanc, P.; Mueller, R.; Pulido, O. *Neurotoxicology* **2003**, *24*, 593.

(4) Bourne, Y.; Radic, Z.; Araoz, R.; Talley, T. T.; Benoit, E.; Servent, D.; Taylor, P.; Molgo, J.; Marchot, P. *Proc. Natl. Acad. Sci.* **2010**, *107*, 6076.

(5) Falk, M.; Burton, I. W.; Hu, T. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron* **2001**, *57*, 8659.

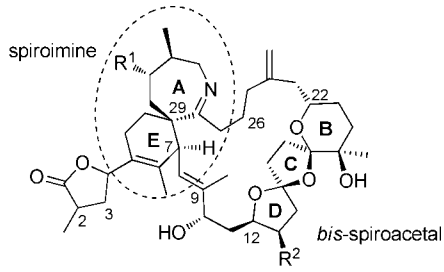
(6) Ciminiello, P.; Catalanotti, B.; Dell'Aversano, C.; Fattorusso, C.; Fattorusso, E.; Forino, M.; Grauso, L.; Leo, A.; Tartaglione, L. *Org. Biomol. Chem.* **2009**, *7*, 3674.

(7) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(8) Ishihara, J.; Ishizaka, T.; Suzuki, T.; Hatakeyama, S. *Tetrahedron Lett.* **2004**, *45*, 7855.

(9) (a) Meilert, K.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 2184. (b) Furkert, D. P.; Brimble, M. A. *Org. Biomol. Chem.* **2004**, *2*, 3573.

10.1021/ol102525w
Published on Web 10/28/2010



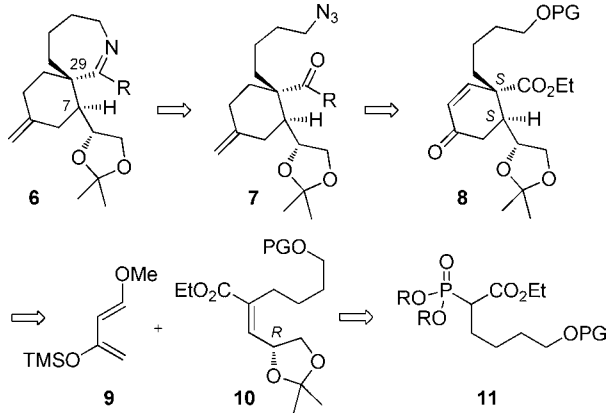
spirolide A (**1**) $\Delta^{2,3}$ R^1 = H, R^2 = Me; **spirolide B** (**2**) R^1 = H, R^2 = Me
spirolide C (**3**) $\Delta^{2,3}$ R^1 = Me, R^2 = Me; **spirolide D** (**4**) R^1 = Me, R^2 = Me
13-desMe spirolide C (**5**) $\Delta^{2,3}$ R^1 = Me, R^2 = H

Figure 1. Relative stereochemistry of the spirolides.

presence of an α-stereocenter in an *anti* relationship to the imine functionality, the synthesis of the spiroimine unit presents a significant synthetic challenge. To date, synthetic approaches to the related pinnatoxins have relied on difficult late-stage imine formation within a macrocyclic framework.[10]

We were interested in investigating the possibility of forming the imine at an earlier stage of the synthesis, to allow a modular approach for assembly of the final macrolide from component fragments. Our strategy aimed to access model spiroimine **6** (Scheme 1) via aza-Wittig

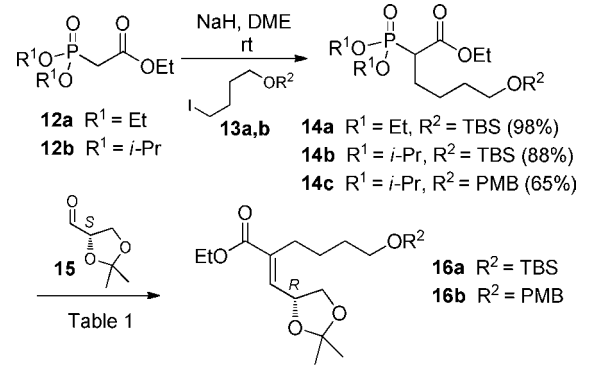
Scheme 1. Retrosynthetic Analysis



cyclization of suitably functionalized keto-azide **7**, derived in turn from cyclohexenone **8**. The required 7*S*,29*S* configuration was envisioned to result from a stereoselective intermolecular Diels−Alder cycloaddition between Danishefsky's diene (**9**) and trisubstituted dienophile **10** prepared from phosphonate **11**. Asano et al.[11] have reported the use of a Diels−Alder reaction between Danishefsky's diene and an (*S*)-trisubstituted dienophile to construct a cyclohexanone containing an α-substituted quaternary center. Other research groups have employed similar strategies with various (*S*)-dienophiles derived from (*R*)-glyceraldehyde acetonide.[12] However, to date, the use of the (*R*)-trisubstituted dienophile derived from (*S*)-glyceraldehyde acetonide in Diels−Alder reactions has not been reported. In addition, synthetically useful asymmetric Diels−Alder reactions of complex trisubstituted dienophiles such as **10** possessing an acyclic α-substituent larger than a methyl group remain relatively uncommon.[13]

Alkylated phosphonates **14a**−**c** were obtained in high yield by treatment of commercially available phosphonates **12a**,**b** with O-protected iodides **13a**,**b**. (*S*)-Glyceraldehyde acetonide **15**[14] was obtained in three steps from commercially available L-ascorbic acid and used immediately. HWE reaction progress, *E*-selectivity, and acetonide epimerization were monitored by RP-chiral-HPLC. Condensation of aldehyde **15** with phosphonate **14a** in the presence of LDA afforded **16a** with racemization of the stereocenter (Table 1, entry 1). HWE performed using

Table 1. Synthesis of (*R*)-Dienophile via a Horner−Wadsworth−Emmons Reaction



entry	R^1	R^2	conditions	yield (%)	*E*/*Z*	racemization
1	Et	TBS	LDA, −78 °C, DME	77	1.1:1	yes
2	Et	TBS	LiHMDS, −50 °C, DME	61	1:1.1	no
3	Et	TBS	DBU, LiCl, rt, MeCN	34	1:1.1	no
4	Et	TBS	*t*-BuOK, −78 °C, DME	78	5.7:1	no
5	***i*-Pr**	**TBS**	***t*-BuOK, −78 °C, DME**	**77**	**7:1**	**no**
6	Et	PMB	*t*-BuOK, −78 °C, DME	90	4.9:1	no

LiHMDS or under Masumune−Roush conditions gave **16a** without racemization but poor *E*/*Z* selectivity (entries 2 and 3). Finally, use of *t*-BuOK afforded the desired dienophiles in high yield with good *E*/*Z* ratios in favor of the *E*-isomer (entries 4−6).

(10) Beaumont, S.; Ilardi, E.; Tappin, N.; Zakarian, A. *Eur. J. Org. Chem.* **2010**, *30*, 5743.

(11) (a) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, *10*, 1539. (b) Asano, M.; Inoue, M.; Watanabe, K.; Abe, H.; Katoh, T. *J. Org. Chem.* **2006**, *71*, 6942.

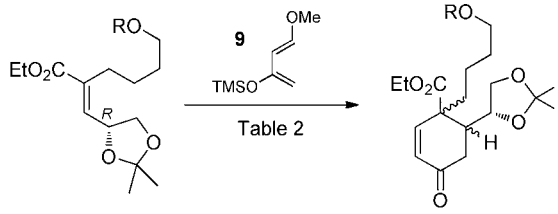
(12) (a) Bunuel, E.; Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1431. (b) Bunuel, E.; Gil, A. M.; Diaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron* **2001**, *57*, 6417. (c) Ortuno, R. M.; Ibarzo, J.; d'Angelo, J.; Dumas, F.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **1996**, *7*, 127. (d) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4983.

(13) Baldovini, N.; Solladié, G. *Tetrahedron: Asymmetry* **2002**, *13*, 885.

(14) Hubschwerlen, C. *J. Org. Chem.* **1991**, *54*, 4056.

The key Diels−Alder reaction between Danishefsky's diene[15,16] (**9**) and **16a** was first attempted using thermal conditions (Table 2).[11] Initial experiments afforded only

Table 2. Diels−Alder Cycloaddition



16a R = TBS (7:1 *E/Z*)
16b R = PMB (4.9:1 *E/Z*)
17a-c R = TBS (*dr* 5:2:1)
18a-c R = PMB

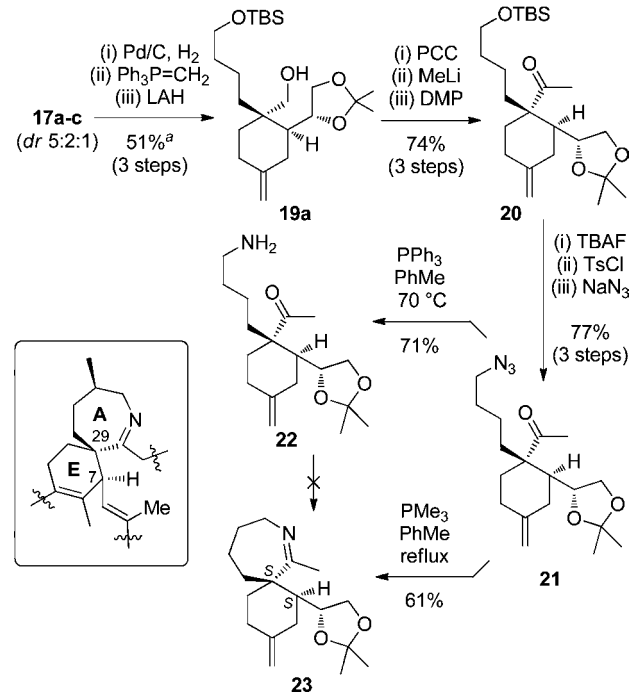
entry	R	solvent	conditions	yield (%)[a]
1	TBS	toluene	sealed tube, 150 °C, 4 days	3
2	TBS	toluene	$Yb(OTf)_3$,[b] rt, 48 h	0[c]
3	TBS	$CHCl_3$	$Eu(fod)_3$,[b] 65 °C, 48 h	0[c]
4	TBS	toluene	$\mu\nu$ 150 °C, 18 h	14
5	**TBS**	**neat**	***μν* 150 °C, 48 h**	**65**[d]
6	PMB	neat	$\mu\nu$ 150 °C, 48 h	35

[a] Yield of **17a−c** or **18a−c** after standard aqueous acid/DBU workup. [b] 20 mol %. [c] sm recovered. [d] ~20% of *E*-dienophile recovered.

traces of the desired cycloadducts **17a−c** (entry 1). Addition of Lewis acids[17,18] failed to give any improvement (entries 2 and 3). However, irradiation of the mixture in toluene[19,20] resulted in a slight increase in yield (entry 4). Solvent-free microwave-assisted conditions proved most successful, affording cycloadducts **17a−c** in 65% yield after acidic workup and elimination of the methoxy group (entry 5). TBS proved to be the most effective protecting group out of those tested (entry 6). Importantly, the optimal conditions proved to be reproducible and scalable, confirming the utility of trisubstituted dienophile **16a**. Standard reduction of the enone proceeded smoothly (Scheme 2). Protection of the ketone as an exocyclic olefin by Wittig methylenation and LAH reduction of the ester to the corresponding alcohol afforded enantiomerically pure major diastereoisomer **19a**, possessing the correct absolute stereochemistry for the spirolides (vide infra).

Alcohol **19a** was next advanced to azido methyl ketone **21** to investigate conditions for the required spiroketimine formation. Previous work in this group has demonstrated the feasibility of imine α-alkylation for later elaboration toward

Scheme 2. Conversion of Diels−Alder Adduct to Spiroimine **23**[a]



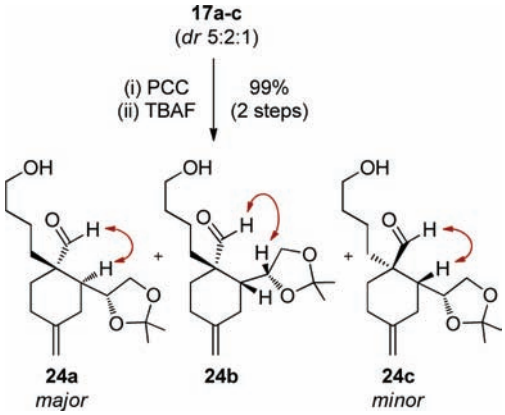
[a] **19b** + **c** (27%) also isolated (see Scheme 3).

the natural product.[21] Disappointingly, initial imine formation attempts using **21** in the presence of triphenylphosphine afforded only keto-amine hydrolysis product **22**. All efforts to cyclize this material using conditions reported for the pteriatoxins[22] and pinnatoxins[23,24] returned only starting material. Pelc and Zakarian[25,26] have reported the successful cyclization of a related keto-azide lacking substitution α to the quaternary center. Accordingly keto-azide **21** was treated with trimethylphosphine in toluene at room temperature then at reflux to afford desired spiroketimine **23** in good yield. **23** proved to be stable in anhydrous toluene or deuterated chloroform for several hours and could be stored for several weeks in the freezer under argon without degradation. The presence of an α-quaternary center and a side chain on the six-membered ring appears to be sufficient to render the imine functionality relatively stable.

To confirm the stereochemical assignment, adducts **17a−c** were converted to corresponding aldehydes **24a−c** for comparison of their respective NOE spectra (Scheme 3). Oxidation with PCC and deprotection using TBAF gave hydroxy aldehydes **24a−c** in excellent yield that were separable by chromatography. The NOESY spectra of the major (**24a**) and minor (**24c**) diastereoisomers supported an *anti* relationship between the aldehyde and the acetonide

(15) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(16) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth., Coll.* **1990**, *7*, 312.
(17) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Pratical Methods*; John Wiley & Sons, Ltd.: Chichester, U. K., 2002.
(18) Jorgensen, K. A. In *Cycloaddition reactions in organic synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2002; p 151.
(19) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363.
(20) Jankowski, C. K.; LeClair, G.; Belanger, J. M. R.; Pare, J. R. J.; VanCalsteren, M.-R. *Can. J. Chem.* **2001**, *79*, 1906.
(21) Brimble, M. A.; Gorsuch, S. *Aust. J. Chem.* **1999**, *10*, 965.
(22) Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 7463.
(23) Matsuura, F.; Hao, J.; Reents, R.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3327.
(24) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774.
(25) Pelc, M. J.; Zakarian, A. *Org. Lett.* **2005**, *7*, 1629.
(26) Pelc, M. J.; Zakarian, A. *Tetrahedron Lett.* **2006**, *47*, 7519.

Scheme 3. Stereochemical Determination of Diels−Alder Diastereoisomers (Key NOE Correlations Shown)

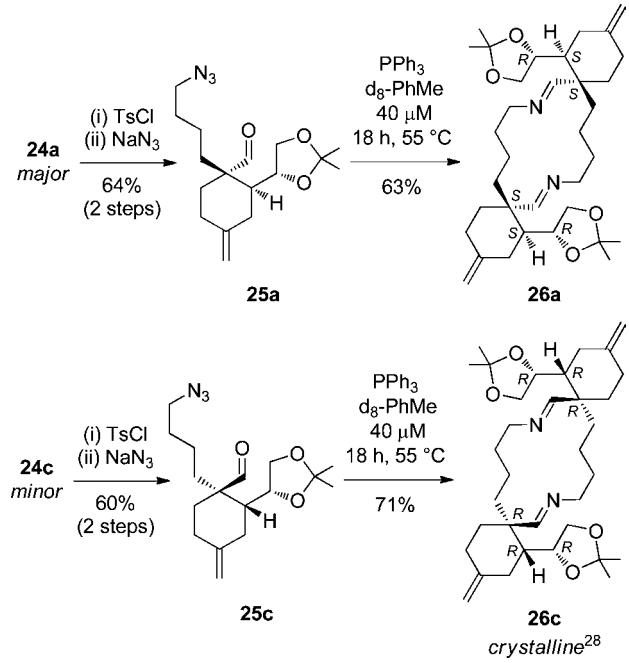


groups, both resulting from Diels−Alder reaction of the *E*-isomer of dienophile **16a**, with the diene preferentially approaching from the less hindered *Si* face as expected. A *syn* relationship between the aldehyde and acetonide in diastereoisomer **24b** resulted from reaction of the minor *Z*-isomer component of dienophile **16a**.[27]

Our earliest efforts to explore intramolecular imine formation had involved advanced azido aldehydes **25a** and **25c**, obtained from primary alcohols **24a** and **24c** by tosylation and nucleophilic displacement with sodium azide (Scheme 4). Attempted cyclizations using triphenylphosphine were conducted in toluene-d_8 to allow NMR monitoring. After warming overnight at 55 °C, only the unexpected stable 14-membered aldimine dimers **26a** and **26c** were isolated. The minor diastereoisomer **26c** proved to be crystalline with the X-ray structure confirming all stereocenters to be *R*, opposite to that required for the spirolides.[28] This information, along with additional NOESY studies,[29] confirmed that major dialdimine **26a**, and therefore also spiroimine **23**, possessed the desired 7*S*,29*S* configuration necessary for the spiroimine unit of the spirolides.

(27) See Supporting Information for NOESY spectra of **24a**−**c**.
(28) Guéret, S. M.; Boyd, P. D. W.; Brimble, M. A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2010**, *E66*, o1778.
(29) See Supporting Information for NOESY spectra of **26a** and **26c**.

Scheme 4. Unexpected Formation of 14-Membered Dialdimines



In conclusion, an efficient approach to enantiopure spiroimine **23** containing both C7 and C29 stereocenters of the spirolides has been developed. This approach also resulted in the preparation of unprecedented stable 14-membered dialdimines **26a**,**c** that allowed unequivocal confirmation of Diels−Alder selectivity by X-ray crystallography. The successful preparation of the 7,6-bicyclic spiroimine represents an important milestone in progress toward the total synthesis of the spirolide family of marine toxins. Further functionalization of the spiroimine unit is currently under investigation.

Supporting Information Available: Experimental procedures, NMR spectra for new compounds, and NOESY spectra for compounds **24a**−**c**, **26a**, and **26c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102525W