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Studies Toward the Synthesis of Spirolides: Assembly of the Elaborated E-Ring Fragment

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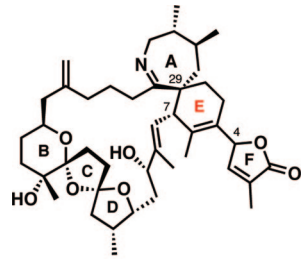
ABSTRACT



Spirolide C

A stereoselective synthesis of the spiroimine fragment of spirolide C is described. The congested C7 and C29 tertiary and quaternary centers are constructed by a diastereoselective Ireland−Claisen rearrangement. The E ring is completed by means of an aldol cyclocondensation. Additional studies were preformed on the advanced intermediate to probe a future coupling strategy.

Spirolides belong to a family of marine toxins isolated from the dinoflagellate *Alexandrium ostenfeldii*, collected from an aquaculture site along the Atlantic coast of Nova Scotia by Wright and co-workers.[1] Spirolides possess a toxicity profile comparable to that of other natural products bearing the characteristic spiroimine moiety, including pinnatoxins,[2] pteriotoxins,[3] and gymnodimine.[4] As established by Wright and co-workers,[1a] the spirocyclic imine appears to be the pharmacophore of these molecules. The absolute stereochemistry of spirolides remains unconfirmed, and the relative configuration of the stereogenic center at C4 has not been assigned.[1]

The spiroimine natural products have generated a high level of interest as targets for chemical synthesis. Several total and one formal syntheses of pinnatoxins and pteriatoxins have been accomplished,[5] and significant progress toward gymnodimine has been achieved.[6] Within this class of natural products, spirolides pose unique challenges for synthesis. In

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(4) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093–7096.

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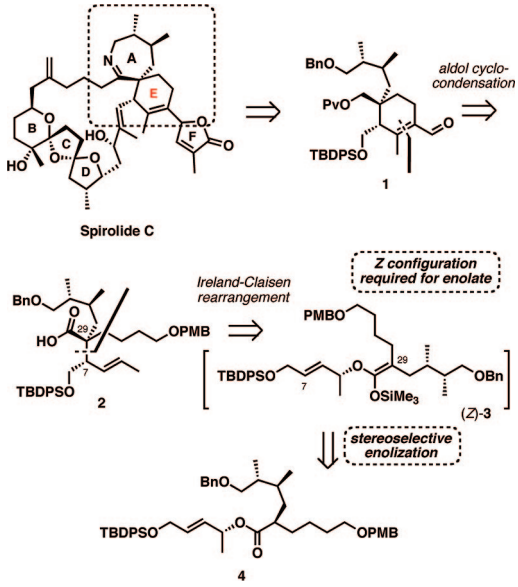
addition to the 6,5,5-dispirotricyclic bisketal, which is only partially stabilized by the anomeric effect, the methyl and butenolide substituents on the double bond of the 6,7-membered spiroimine add to other structural attributes that make spirolides formidable synthetic targets. Several studies aimed at the 6,5,5-dispiroketal portion of spirolides have been described,[7,8] yet progress to the intricate spiroimine fragment has been extremely limited.[9]

Our approach to the spiroimine fragment of spirolides is based on the projected diastereoselective Ireland−Claisen rearrangement of ester **4** followed by aldol cyclocondensation to form the cyclohexene ring incorporating a tetrasubstituted double bond (Scheme 1). Stereoselective generation of the

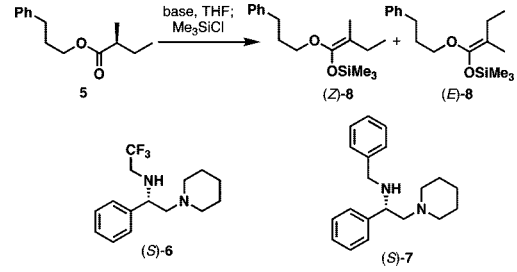
Scheme 1. General Synthesis Plan



(*Z*)-enolate ((*Z*)-**3**) will be required for efficient chirality transfer to the adjacent quaternary and tertiary stereocenters at C29 and C7.

A method for stereoselective enolization of α-branched esters has been recently developed in our laboratory.[10] According to this method, chiral Koga-type bases or other chiral lithium amides are used with stereodefined acyclic α-branched esters to achieve highly stereoselective enolizations. As part of an ongoing investigation to improve stereoselectivity and to define the scope and utility of this technique, we explored new bases, including the lithium amides formed from benzylamines (*S*)-**7**[11] and (*R*)-**7**.[12] Using ester **5**, we compared the stereoselectivity of the enolization to that obtained with lithium amides (*S*)-**6**-Li and (*R*)-**6**-Li produced from trifluoroethylamines (*S*)-**6** and (*R*)-**6**, which showed the highest stereocontrol previously.[10] As depicted in Table 1, (*S*)-**7** and (*R*)-**7** proved to be superior bases for

Table 1. Enolization Study



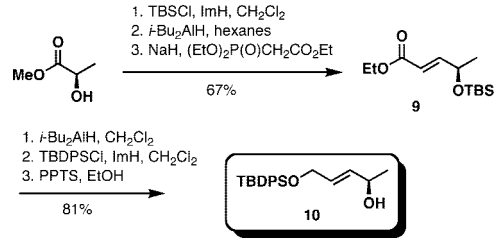
entry	base[a]	(*Z*)-**8**:(*E*)-**8**[b]
1	LDA	67:33
2	(*S*)-**6**-Li	8:92
3	(*S*)-**7**-Li	2:98
4	(*R*)-**6**-Li	92:8
5	(*R*)-**7**-Li	96:4

[a] LDA = lithium diisopropylamine. [b] The ratio of isomers was determined by 500 MHz ^{1}H NMR of the crude mixture of products.

stereoselective enolization of **5**. Thus, switching from (*S*)-**6** to (*S*)-**7** improved selectivity from 92% to 98%, favoring the (*E*)-enolate. In the (*R*)-series, moving from amine **6** to **7** improved *Z*-selectivity from 92% to 96%. These observations demonstrate that the benzyl base **7** overall exerts a stronger stereodirecting effect in both matched and mismatched cases. Another practical advantage is that benzylamine **7** is considerably more convenient in terms of preparation and handling. It is a crystalline solid which requires benzylamine rather than expensive trifluoroethylamine for its synthesis.

With these results at hand, the synthesis of ester **4** commenced with the preparation of allylic alcohol **10** from commercially available (*R*)-(+)-methyl lactate (Scheme 2). Protection of the hydroxyl group as *tert*-butyldimethylsilyl ether followed by reduction of the methyl ester and olefi-

Scheme 2. Synthesis of Allylic Alcohol **10**



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(7) (a) Meilert, K.; Brimble, M. A. *Org. Lett.* **2005**, *7*, 3497–3500. (b) Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2002**, *4*, 3655–3658. (c) Meilert, K.; Brimble, M. A. *Org. Biomol. Chem.* **2006**, *4*, 2184–2192. (d) Brimble, M. A.; Caprio, V.; Furkert, D. P. *Tetrahedron* **2001**, *57*, 4023–4034. (e) Brimble, M. A.; Fares, F. A.; Turner, P. *Aust. J. Chem.* **2000**, *53*, 845–851.

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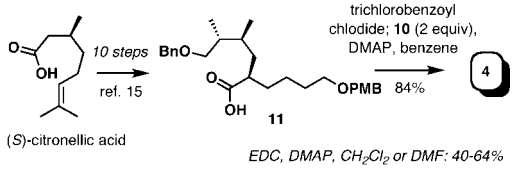
nation of the resulting aldehyde afforded ester **9**.[13] Reduction of the ethyl ester to the allylic alcohol with *i*-Bu_2AlH followed by protection of the hydroxyl group as the *tert*-butyldiphenylsilyl ether and selective ethanolysis of the TBS protecting group with pyridinium *p*-toluenesulfonate delivered allylic alcohol **10** in six steps,[14] in good yield, and with only two chromatographic purifications.

Carboxylic acid **11** was prepared previously on a multigram scale by a ten-step route starting from (*S*)-citronellic acid (Scheme 3).[15] After briefly exploring different reaction

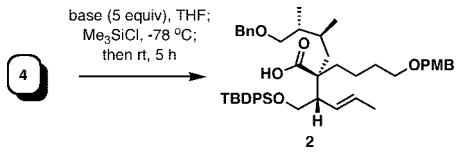
Scheme 3



conditions for esterification of carboxylic acid **11** with allylic alcohol **10** (EDC, DMAP, DMF, or CH_2Cl_2), we determined that the Yamaguchi conditions were more effective in delivering ester **4** in good yield.[16]

The studies on the Ireland−Claisen rearrangement of ester **4** revealed suprising results. As anticipated, the application of the chiral lithum amides generated from either (*S*)-**6** or (*S*)-**7** accomplished the desired rearrangement in high yield and excellent diastereoselectivity. In accord with our previous experience with esters of **4**,[5b,10] 5 equiv of these bases is required for complete enolization. Remarkably, when LDA was employed the rearrangement also occurred with high diastereoselectivity, albeit in significantly lower yields (Table 2). In this case, various quantities of carboxylic acid **11** were

Table 2. Enolization/Rearrangement Study

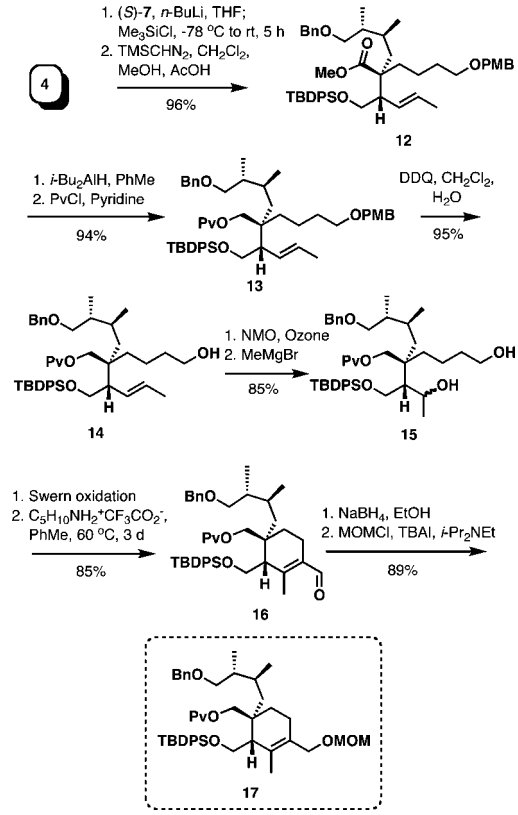


entry	base	isolated yield
1	LDA	37%
2	(*S*)-**6**-Li	84%
3	(*S*)-**7**-Li	94%

recovered (25−35%), presumably because fragmentation of the lithium enolate generated using LDA is competitive with the O-silylation with Me_3SiCl.[17] Despite numerous attempts under varying reaction conditions,[18] the enolization−rearrangement was consistently low yielding with LDA. On the other hand, with the lithium amide of (*S*)-**7**, highly diastereoselective, efficient, scalable, and reproducible Ireland−Claisen rearrangement was observed. Chiral amine (*S*)-**7** can be recovered in quantitative yield by a simple extraction with aqueous acid if desired.

Continuing with our synthetic studies toward spirolides, the Ireland−Claisen rearrangement of ester **4** followed by treatment of the crude product with (trimethylsilyl)diazomethane afforded methyl ester **12** in 96% yield over the two steps (Scheme 4).[19] Chiral amine (*S*)-**7** was recovered

Scheme 4. Synthesis of the E-Ring



in quantitative yield by extraction with aqueous hydrochloric acid.

Reduction of the methyl ester with *i*-Bu_2AlH and protection of the primary alcohol delivered pivaloate **13**. Oxidative

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(18) Varying concentration, number of equivalents of LDA, and reaction time led to decomposition and/or incomplete reactions.

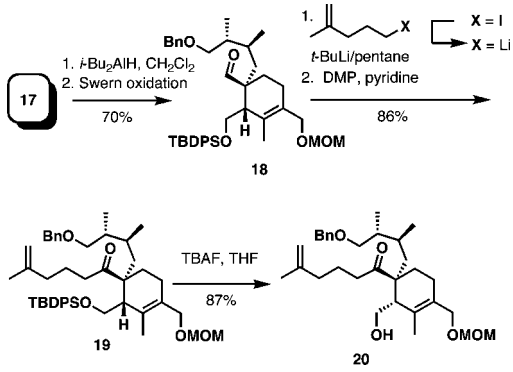
(19) For a recent review on (trimethylsilyl)diazomethane, see: Kühnel, E.; Laffan, D. D.; Lloyd-Jones, G. C.; del Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075–7078.

removal of the PMB protecting group with DDQ furnished alcohol **14** in high yield. Ozonolysis of **14** directly to the corresponding hydroxy aldehyde in the presence of *N*-methylmorpholine[20] followed by the addition of methylmagnesium bromide delivered diol **15** as a mixture of diastereomers in good yield.

Double oxidation of the diol **15** to the corresponding keto aldehyde set the stage for an aldol cyclo-condensation, which was accomplished in the presence of piperidinium trifluoroacetate in toluene at 60 °C for 3 days, affording the desired cyclized intermediate **16** in 85% yield over two steps.[5b,21] Reduction of the enal with sodium borohydride and protection of the resulting primary alcohol as the methoxymethyl ether completed the synthesis of the advanced intermediate **17**.

The subsequent transformations, illustrated in Scheme 5, were carried out to explore the viability of the future fragment

Scheme 5



coupling en route to spirolides. We plan to achieve a fragment union by a straightforward addition of an advanced organolithium reagent to a hindered aldehyde such as **18** with a subsequent reoxidation of the addition product. Thus, reductive cleavage of the pivaloate ester in **17** with *i*-Bu_2AlH followed by oxidation of the resulting primary alcohol delivered the desired aldehyde **18** in good yield. Gratifyingly, the organolithium reagent produced from 1-iodo-4-methyl-4-pentene via iodine−lithium exchange underwent a smooth addition to **18**,[22] delivering the secondary alcohols as a mixture of diastereomers. Oxidation of the alcohols with Dess-Martin periodinane provided ketone **19** in an 86% overall isolated yield over the two steps (Scheme 5).[23] Finally, the removal of the TBDPS group was accomplished using TBAF, delivering **20** in 87% yield.

In summary, we have described an efficient, enantioselective synthesis of the cyclohexene ring E of spirolides incorporating the challenging adjacent tertiary and quaternary stereocenters at C7 and C29. These stereogenic centers were constructed with high stereocontrol by a single diastereoselective Ireland−Claisen rearrangement employing a method recently developed in our laboratory. Aldol cyclocondensation proved to be a powerful tactic for the assembly of the tetrasubstituted double bond in ring E. Subsequent studies demonstrated viability of the future fragment coupling strategy based on organolithium addition to aldehyde **18**.

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Supporting Information Available: Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra for compounds described in this report. This material is available free of charge via the Internet at http://pubs.acs.org.

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