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Synthesis of the C1–C20 and C15–C27 Segments of Aplyronine A

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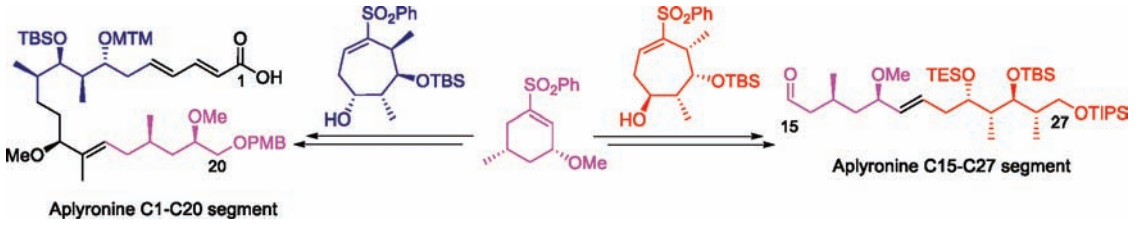
ABSTRACT



The synthesis of C1–C20 and C15–C27 segments of Aplyronine A is described. Oxidative cleavage of cyclic vinyl sulfones has been used to prepare key fragments of Aplyronine A. Key precursors are united by Horner–Wadsworth–Emmons and Julia–Kociensky olefination for the respective elaboration of the C1–C20 and C15–C27 segments.

Aplyronine macrolides were first isolated in 1993 from the sea hare *Aplysia kurodai* collected on the Japanese coast.[1] Among them, aplyronine A (Figure 1) exhibited potent cytotoxicity against HeLa S3 cells with an IC_{50} of 0.48 ng/mL and impressive antitumor activities against various cell lines.[2] Although aplyronine inhibits polymerization of actin[3] and the X-ray cocrystal structure of aplyronine A•actin is known, micromolar concentrations are necessary to depolymerize actin. Nanomolar concentrations show *in vivo* anticancer activity, suggesting that aplyronine A exerts its antineoplastic activity via a yet-to-be-deteremined mechanism.

To date, only one total synthesis of aplyronine A has been reported by Yamada et al.[4] Recently, Kigoshi reported the synthesis of the C1–C19 segment, featuring an asymmetric Nozaki–Hiyama–Kishi (NHK) coupling reaction.[5] Apart from these two syntheses, there have been several reports directed toward aplyronine A.[6]

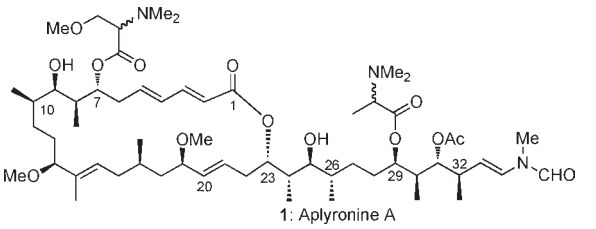


Figure 1. Aplyronine A: mixture of four side chain diastereomers.

Aplyronine A is an attractive synthetic target bearing three stereotetrads (dipropionates): (C7–C10) is *anti, syn, anti* while (C23–C26 and C29–C32) bear *anti, anti, syn* stereochemistries. Recently, all eight possible diastereomeric cyclic stereotetrads were prepared from enantiopure cycloheptadienyl sulfones via a diastereoselective epoxidation/methylation sequence.[7] Specifically, it was demonstrated that oxidative cleavage of cyclic stereoenriched vinyl sulfones afforded the requisite termini-differentiated fragments, *viz* C5–C11, C15–C20, C21–C27, and C28–C34 of aplyronine A.[8]

(1) Syntheses via Vinyl Sulfones 101. Chiral Carbon Catalog 23. For review on aplyronine natural products, see: Yamada, K.; Ojika, M.; Kigoshi, H.; Suenaga, K. *Nat. Prod. Rep* **2009**, *26*, 27.

(2) (a) Yamada, K.; Ojika, M.; Ishigaki, T.; Yoshida, Y.; Ekimoto, H.; Arakawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 11020. (b) Ojika, M.; Kigoshi, H.; Ishigaki, T.; Tsukada, I.; Tsuboi, T.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7441.

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(4) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443.

(5) Kobayashi, K.; Fujii, Y.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2011**, *13*, 900.

(6) (a) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037. (b) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041. (c) Paterson, I.; Blakey, S. B.; Cowden, C. J. *Tetrahedron Lett.* **2002**, *43*, 6005. (d) Calter, M. A.; Guo, X. *Tetrahedron* **2002**, *58*, 7093. (e) Calter, M. A.; Zhou, J. *Tetrahedron Lett.* **2004**, *45*, 4847. (f) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501.

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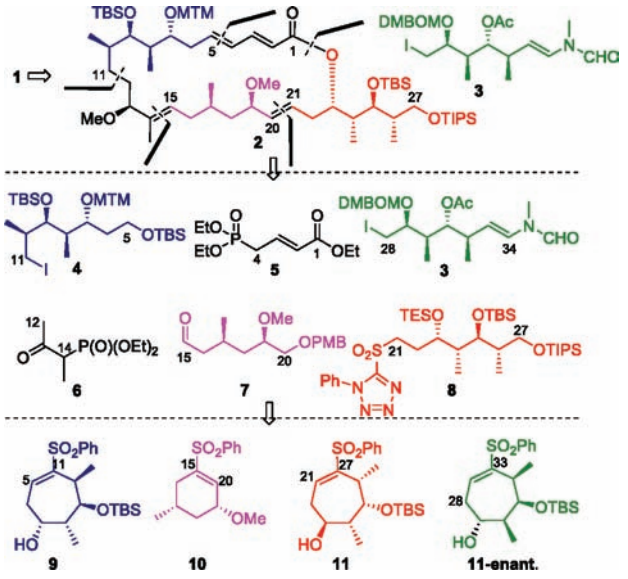
Herein we communicate the advancement of two stereotetrads to an acyclic intermediate and its union with other segments to yield the C1−C20 and C15−C27 segments of aplyronine A.

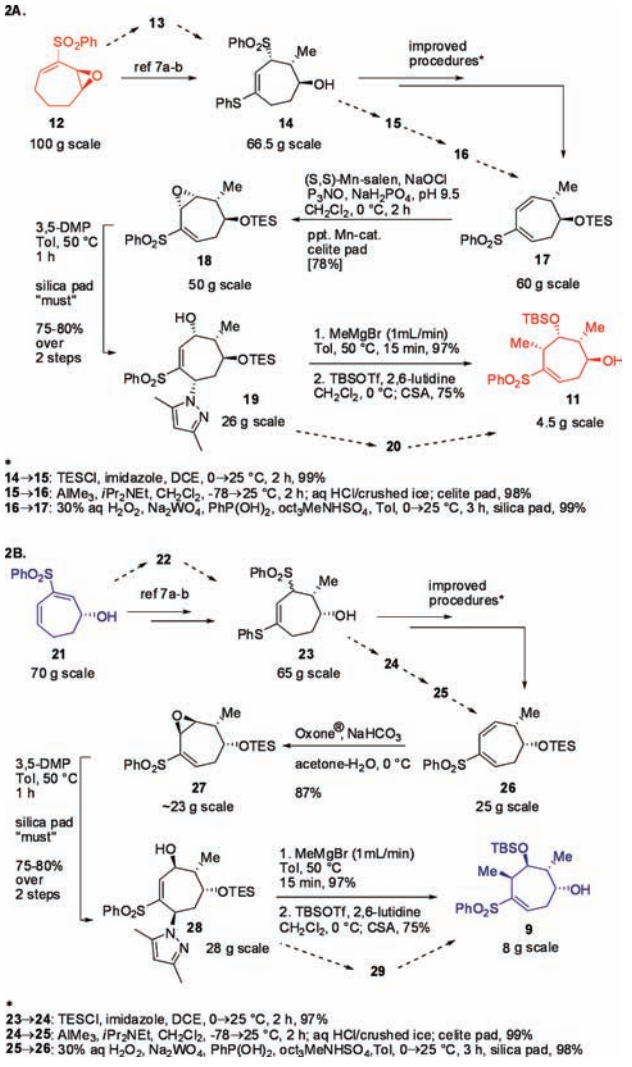
Scheme 1. Retrosynthetic Analysis



As outlined in Scheme 1, the synthetic approach is based on the disconnection of macrocyclic lactone **2** and side chain **3**. Macrocyclic core **2** is accessed from building blocks **4**, **5**, **6**, **7**, and **8**. Segments **4**, **7**, and **8** are derived by vinyl sulfone strategies creating stereodefined polypropionate fragments. Side chain **3** was projected to be constructed from **11-enantiomer**.

To obtain stereotetrads **9** and **11** reproducibly, a strategic protecting group switch from −OTBS to −OTES was crucial to avoid problems in regioselective deprotection of the final bis-OTBS stereotetrad.[9] Epoxide **12** was converted to vinylsulfide **14** on a 100 g scale. Improved procedures based on our previous report[7a] afforded dienylsulfone **17** on a 60 g scale. In contrast to our previous methodology, it was observed that early −OTES protection (**14** to **15**) performed better for the elimination to dienylsulfide **16** employing $AlMe_3$. Jacobsen epoxidation of **17** proved challenging due to rapid onset followed by stalling after 72 h. Adding more catalyst and/or oxidant resulted only in product decomposition.[10] It was envisaged that an increase of the concentration of the actual oxidant [HOCl] was required. After extensive experimentation at different pH ranges,[11] pH 9.0−9.5[12] was found to be optimal for clean conversion to **18** in 2 h.

Scheme 2. Large Scale Synthesis of **11** and **9**[13]



Due to the sensitivity of **18** to silica, removal of the Mn-salen without chromatography was crucial. Conveniently, adding hexanes (300% v/v) quantitatively precipitated the Mn-salen, cleanly affording **18** after pad filtration.[14] After treating **18** with 3,5-dimethylpyrazole (DMP), silica filtration of adduct **19** was a "must" due to the sensitivity of the next reaction. *Syn*-directed methylation to **20** was not trivial.[15] The best procedure employed

(7) (a) Noshi, M. N.; El-Awa, A.; Fuchs, P. L. *J. Org. Chem.* **2008**, *73*, 3274. (b) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315. (c) El-Awa, A.; Mollat du Jourdin, X.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 9086. (d) Hong, W. P.; El-Awa, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2009**, *131*, 9150.

(8) (a) El-Awa, A.; Fuchs, P. L. *Org. Lett.* **2006**, *8*, 2905. (b) Noshi, M. N.; El-Awa, A.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 11242.

(9) For such deprotection, a delicate balance must be achieved between TBAF and MeOH. While excess TBAF resulted in elimination and lack of regioselectivity, excess MeOH completely deactivated TBAF. Thus it was not a "robust" process for scale-up purposes.

(10) For similar observations, see: Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.

(11) For buffer preparation and pH calculation, see Table 1 in Supporting Information.

(12) At this pH range, no chlorinated products were observed.

(13) See detailed experiments and extended discussion in the Supporting Information.

(14) See Figure 3 in Supporting Information.

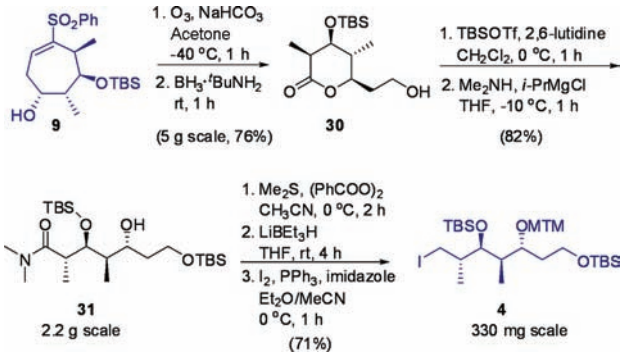
(15) Adding MeMgBr at 23−35 °C resulted in partial conversion and stalling. Adding more MeMgBr resulted in over methylation of **20** rather than **19**. See optimization Table 2 in Supporting Information.

treating **19** at 50−60 °C with MeMgBr at rates of 1−2 mL/min, effecting clean conversion to **19**. Treatment with TBSOTf, followed by chemoselective deprotection of −OTES, afforded stereotetrad **11** on scales up to 4.5 g (Scheme 2A). Similarly, alcohol **21** was converted to stereotetrad **9** on scales up to 8 g (Scheme 2B).

Fragment **4**, possessing the stereotetrad (C7−C10), can be obtained from cyclic vinyl sulfone **9**. Similarly, fragment **8** with C23−C26 can be prepared from cyclic vinyl sulfone **11**. Following our previous report, fragment **10** was chosen to introduce the C15−C20 array **7**. Notably, β-ketophosphonate **6** was adopted for joining iodide **4** and aldehyde **7** as developed by Paterson and Calter.[6b,6e]

The synthesis starts with vinyl sulfone **9** which was converted to lactone **30** upon ozonolysis followed by reductive workup (Scheme 3). After protection of the primary alcohol in **30** as the silyl ether, the lactone was converted to acyclic dimethylamide[16] **31** using a protocol developed for making Weinreb amides.[17] Interestingly, synthesis of the specific methoxymethyl amide failed under these conditions. Super-Hydride ($LiBEt_3H$) reduction of the dimethylamide yielded the primary alcohol[18] in virtually quantitative yield, which was subsequently converted to iodide **4** (71% yield over three steps).

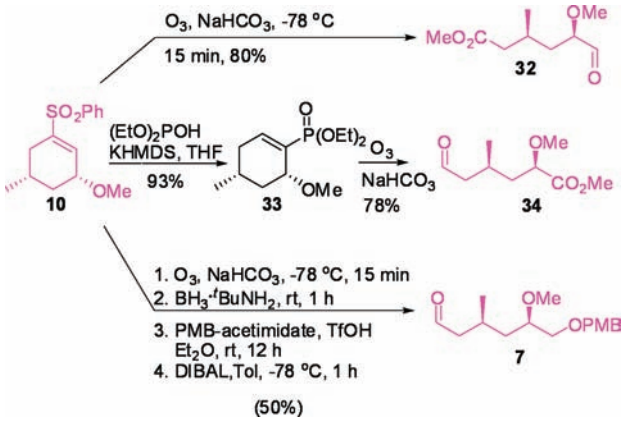
Scheme 3. Synthesis of Iodide **4**



The synthesis of the C15−C20 target starts with known vinyl sulfone **10** that underwent ozonolysis to give acyclic ester-aldehyde **32** as the Julia−Kocienski olefination substrate (Schemes 4 and 6).[8b]

In 2007, our group reported a variant of the Taber reaction,[19] in which cyclic vinyl sulfone **10** was converted to transposed vinyl phosphate **33** featuring a formal end-for-end REDOX transposition. Treatment of **10** with the sodium salt of diethylphosphite gave vinyl phosphonate **33** in 93% yield. Oxidative cleavage of **33** provided aldehyde-ester **34** desired for the Horner−Wadsworth−Emmons (HWE) coupling step (Schemes 4 and 7). Handling aldehyde-ester **34** was quite troublesome since it was exceptionally prone to air oxidation giving the carboxylic acid. Fortunately, it was found that aldehyde-PMB ether **7** is inert to air oxidation. The aldehyde **7** was obtained in four steps from vinyl sulfone **10** (Schemes 4 and 7).

Scheme 4. Synthesis of C15−C20 Terminii-Differentiated Segments[a]



[a] Ozonolysis was performed in CH_2Cl_2/MeOH (4:1).

The synthesis of C21−C27 intermediate **8** commences with ozonolysis[20] of **11** followed by reduction to afford lactone-alcohol **35** (Scheme 5). DCAD Mitsunobu coupling[21] of **35** followed by lactone opening generated Weinreb amide **37**, which was transformed to alcohol **38** via the intermediate aldehyde. Initial attempts to protect the alcohol with a benzyl group were unsuccessful due to the TBS migration and TES deprotection. To circumvent these difficulties, TIPS protection was adopted. Final *m*-CPBA oxidation delivered the C21−C27 fragment sulfone **8**.

With **8** and **32** in hand, Julia−Kocienski olefination (Scheme 6) was investigated to construct the C15−C27 subunit of aplyronine A. Low E/Z ratios were obtained, using Li or KMHDS in THF (entries 1 and 3). Changing the solvent to DME[22] gave a better ratio (E/Z = 5.5:1) (entry 2). Much to our delight, application of Jacobsen's solvent combination (DMF/HMPA)[23] gave the best selectivity (E/Z = 12:1) in a yield of 60%, 83% based upon recovered starting material. Subsequent DIBAL reduction afforded aldehyde **40** in 92% yield.

With compounds **4**, **5**, **6**, and **7** in hand, attention was directed to the C1−C20 segment synthesis (Scheme 7). The

(16) Occasionally, quenching with aqueous NH_4Cl resulted in some global elimination. See Figure 5 in Supporting Information for suggested mechanism and characterization.

(17) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(18) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(19) Taber, D. F.; Saleh, S. A. *J. Org. Chem.* **1981**, *46*, 4817.

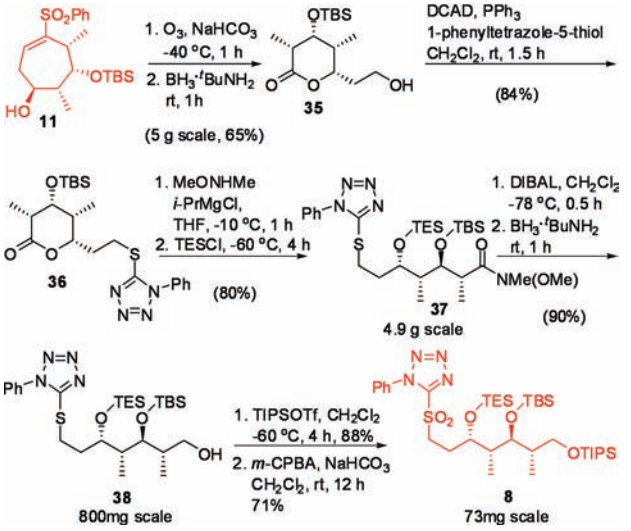
(20) Ozonolysis was performed successfully in CH_2Cl_2 and in acetone, based on "the added aldehyde effect". For ozonolysis in acetone, see: (a) Su, J.; Murray, R. W. *J. Org. Chem.* **1980**, *45*, 678. (b) Schiaffo, C. E.; Dussault, P. H. *J. Org. Chem.* **2008**, *73*, 4688. (c) For stabilization of carbonyl oxide with acetone, see Figure 4 in Supporting Information.

(21) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral, R. *Org. Lett.* **2006**, *8*, 5069.

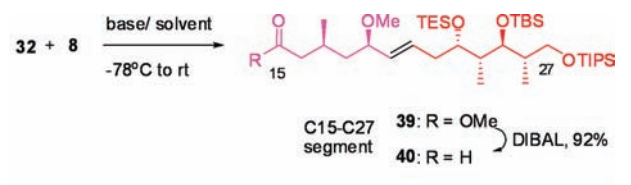
(22) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26.

(23) (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. (b) Smith, A. B.; Dong, S.; Brenneman, J. B.; Fox, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 12109.

Scheme 5. Synthesis of C21−C27 Tetrazole Sulfone **8**



Scheme 6. Julia−Kociensky Olefination of Fragment **8** and **32**[a]

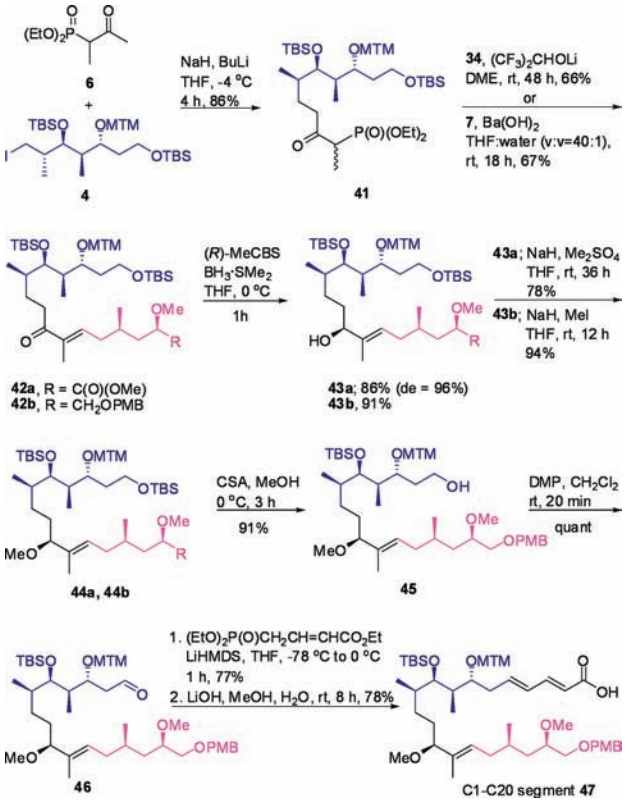


entry	base	solvent	yield (%)[a]	*E*:*Z*[b]
1	KHMDS (0.5M toluene)	THF		1:1
2	KHMDS (0.5M toluene)	DME	56 (77 brsm)	5.5:1
3	LiHMDS (1M THF)	THF		2:1
4	LiHMDS (1M THF)	DMF/ HMPA (4:1 v/v)	60 (83 brsm)	12:1

[a] Isolated yields (entries 1 and 3) were not calculated due to the low *E*/*Z* selectivity. [b]Determined by crude 1H NMR.

sodium/lithium dianion of *β*-ketophosphonate **6** reacted smoothly with iodide **4** to give **41** in 86% yield. HWE reaction with **34** was performed best using Myer's protocol[24] affording enone **42a** in 66% yield.[25] When barium hydroxide mediated HWE coupling[6b] was utilized with **7**, a similar yield (67%, 77% based upon recovered starting material) was obtained providing enone **42b**. Chemo- and stereoselective reduction of enones **42a**, **42b** to alcohols **43a**, **43b** respectively was achieved using the (*R*)-MeCBS[26] catalyst (**43a**; de = 96%). The absolute stereochemistries of product **43a** were determined by analysis of the ^{1}H NMR of their Mosher's esters.[27] Methylation of the secondary alcohol was achieved using sodium hydride and dimethyl sulfate or methyl iodide giving **44a** (78%) and **44b** (94%), respectively. Deprotection of the primary TBS group in **44b** using 10 mol % CSA gave **45** in 91% yield.

Scheme 7. Synthesis of C1−C20 Carboxylic Acid **47**



Application of Kigoshi's oxidation of **45**,[28] followed by α,*β*,*γ*,*δ*-unsaturated ester formation (LiHMDS[29] and $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$), led to the C1−C20 segment of aplyronine A as a 4*E*/4*Z* mixture (12:1). Finally, completion of the C1−C20 acid **47** was achieved by LiOH hydrolysis in 78% yield.

In conclusion, synthesis of the C1−C20 and C15−C27 segments of aplyronine A was accomplished via a convergent strategy. The use of vinyl sulfone chemistry was pivotal for the synthesis of three key precursors. The total synthesis and biological activity of aplyronine A analogs will be communicated in due course.

Acknowledgment. We thank Dr. Karl Wood and Dr. Douglas Lantrip (Purdue University) for providing MS and HPLC data.

Supporting Information Available. Spectroscopic (^{1}H NMR, ^{13}C NMR, HRMS), analytical data, and experimenatal details. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281.

(25) The (*E*) stereochemistry of the newly formed double bond was confirmed by NOE difference spectroscopy, and the (*Z*) stereoisomer was not observed in the crude mixture.

(26) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(27) See Supporting Information.

(28) Partial MTM elimination (enal formation) was observed with a Dess−Martin periodinane (DMP)/10 equiv pyridine reaction.

(29) HWE reaction with LDA, employed by the Kigoshi group in their approach to the C1−C19 segment of Aplyronine A, afforded dienoate in 86% yield with 5% (4*Z*)-isomer; see ref 5.