A Flexible Synthetic Approach to the Hennoxazoles

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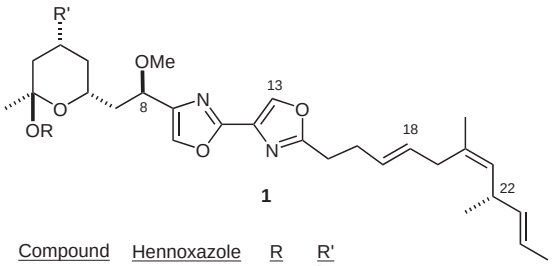
Abstract: Three advanced intermediates corresponding to the carbon skeleton of the hennoxazoles have been prepared. Central to the strategy is the synthesis of the oxazoles prior to coupling with the other fragments and a dithiane addition to allow for the generation of diastereomers of the natural product.

Key words: hennoxazole A, isopentylidene, bisoxazole, β,γ-unsaturated aldehyde, skipped polyene

In 1990, Scheuer and Higa isolated a series of alkaloids from *Polyfibrospongia sp.*, a marine sponge collected near the island of Miyako, Japan.[2] They named these natural products the hennoxazoles, and the most abundant member of this family, hennoxazole A (**1a**, Figure 1) was found to display antiherpetic and analgesic activity. Subsequent work by Higa provided several additional hennoxazoles in which the only differences were within the C1–C8 polyol region.[3] The initial structural assignments only established the relative configuration about the pyran ring, while the absolute stereochemistry of the pyran, C8, and C22 remained unknown.

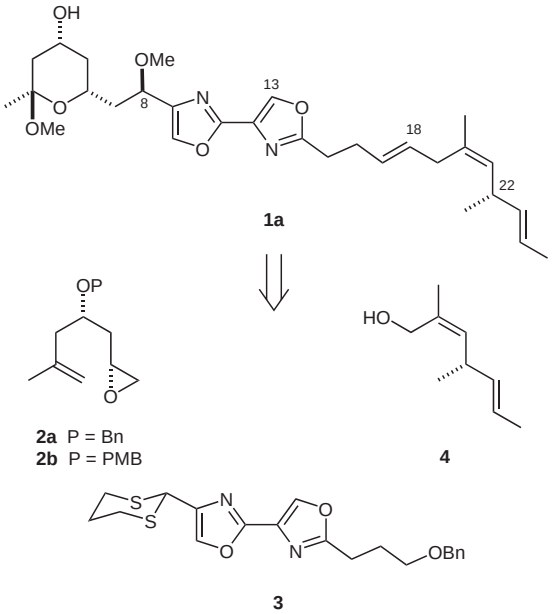


Compound	Hennoxazole	R	R'
1a	A	Me	OH
1b	B	Et	OH
1c	C	Bu	OH
1d	D	Me	H
1e	E	H	OH

Figure 1 The hennoxazoles A–E

This structural ambiguity and intriguing bioactivity has prompted considerable synthetic attention.[4] Wipf identified the absolute stereochemistry of the hennoxazoles by his synthesis of *ent*-hennoxazole A (*ent*-**1a**),[5] while Williams subsequently completed the first synthesis of the natural enantiomer.[6] Barrett[7] and Smith[8] have described the construction of model bisoxazoles simulating the central portion of the hennoxazoles, while Shioiri has published the synthesis of several key intermediates, culminating in a total synthesis of the natural enantiomer of hennoxazole A (**1a**).[9] These results have prompted us to disclose our own efforts toward a unified total synthesis of the hennoxazoles.

Retrosynthetically, we disconnected the molecule at the C7–C8 and C18–C19 bonds, leading to three disparate fragments: epoxide **2**, bisoxazole **3** and skipped diene **4** (Scheme 1). These disconnections were chosen to allow easy variation of the stereochemistry at C8 and C22. After introduction of C8 as a protected carbonyl, a stereoselective reduction and subsequent methylation would allow access to either potential diastereomer. Osmylation, periodate cleavage, and ketalization at C2 would afford the hydropyran, while alkynylation to incorporate C18 and palladium coupling with a diene derived from **4** would complete the carbon skeleton. Ketalization with the appropriate alcohol would provide hennoxazoles A–C and E, while reductive deoxygenation of **1** would lead to hennoxazole D.



Scheme 1 Retrosynthetic analysis of hennoxazole A (**1a**)

The synthesis of the epoxide fragment began from readily available (*R*)-1,2,4-butanetriol (**5**, Scheme 2).[10] Selective 1,2-ketalization[11] with 3-pentanone was followed by 2,2,6,6-tetramethylpiperidinooxy (TEMPO)-catalyzed oxidation[12] to give volatile aldehyde **6**. Direct stereochemical induction from the β-stereocenter of **6** is quite

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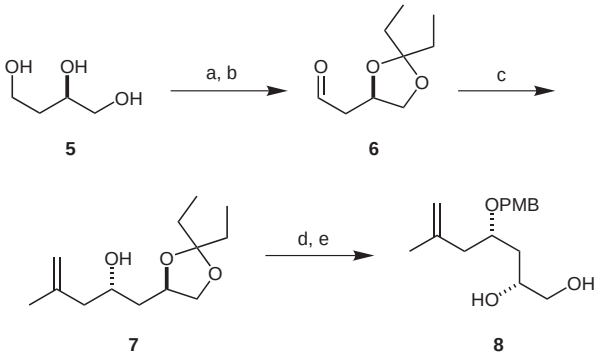
poor, but a catalytic chiral methallylation afforded **7** in 90% de.[13] Protection of the alcohol as a benzyl or *p*-methoxybenzyl ether was followed by deketalization to provide the diol **8**.[14] This compound served as the precursor to epoxide **2** in a one-pot epoxidation and dithiane coupling (vide infra).



Scheme 2 Synthesis of epoxide precursor **8**. *Reagents and conditions*: (a) $(MeO)_3CH$, *p*-TsOH, Et_2CO, MeOH–CH_2Cl_2 (2:1), reflux, 87%; (b) TEMPO, KBr, aq $NaHCO_3$, NaOCl, aq $NaHCO_3$, brine, H_2O– CH_2Cl_2, 0 °C, 75%; (c) methallyl tributylstannane, Ti(O*i*-Pr)$_4$, (*R*)-BINOL, CH_2Cl_2, 0 °C to –20 °C, 63%; (d) (i) NaH; (ii) PMBBr, THF–DMF (3:1), 69%; (e) Dowex 50WX8 H^+ resin, MeOH, 62%.

The central bisoxazole fragment[15] was prepared from acid **9** (Scheme 3), readily available from γ-butyrolactone.[16] Following coupling with serine methyl ester,[17] the amide product **10** was cyclized[18] and aromatized[19] to give oxazole **11**. The subsequent construction of the second oxazole ring proved to be considerably more difficult than we had originally anticipated. While a second serine residue could be added efficiently, all attempts to activate the corresponding alcohol resulted in elimination and formation of acrylate **13** (Figure 2). Ultimately, the second oxazole was incorporated using methodology developed by Shapiro.[20] Amidation of **11** with malonate **12** gave **14**, which cyclized to the corresponding bisoxazole **15**. Finally, reduction of the ester[21] and conversion to a dithiane[22] yielded the central fragment **3**.[23]

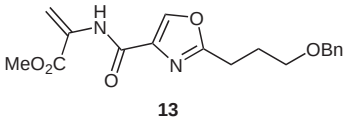
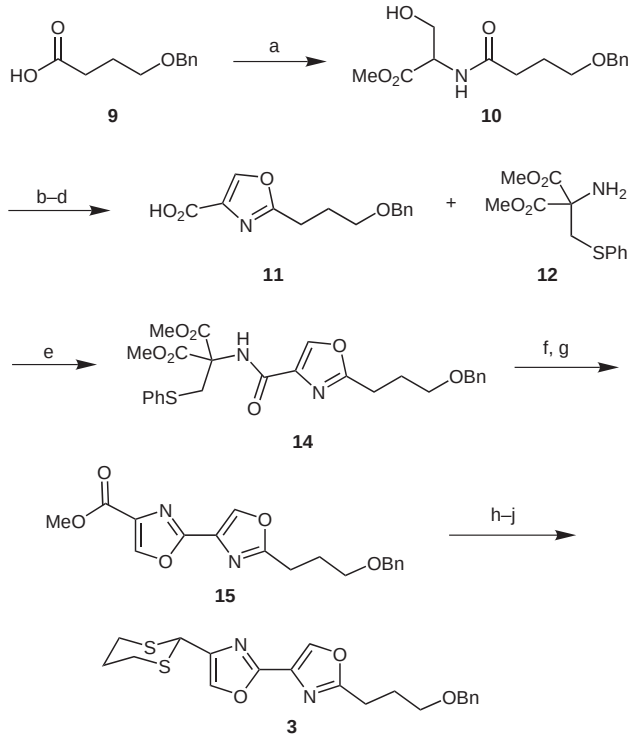


Figure 2

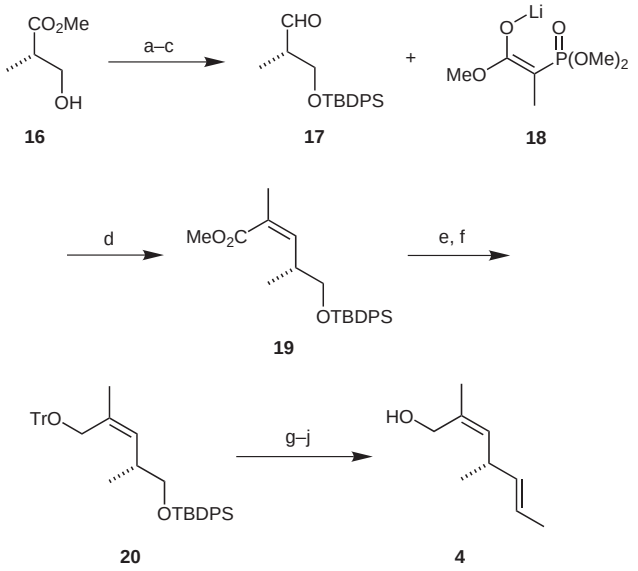
A key constraint in the synthesis of the diene fragment was the then-unknown stereocenter at C22. Therefore, we chose a path that originated from a chiral pool member that was readily available in either enantiomer; in fact, both enantiomers of **4** were prepared by the route shown (Scheme 4). Propionate **16** was transformed into aldehyde **17**[24] by standard procedures, and Horner–Emmons olefination with α-methylphosphonate **18**[25] gave 11:1 selectivity for the *Z*-alkene **19**.[26] Following reduction of the isomeric mixture with DIBAL-H,[27] tritylation afforded



Scheme 3 Synthesis of bisoxazole dithiane **3**. *Reagents and conditions*: (a) (i) Et_3N, *t*-BuCOCl, DMAP; (ii) serine methyl ester hydrochloride, CH_2Cl_2, 67%; (b) PPh_3, CCl_4, *i*-Pr_2NEt, MeCN–CH_2Cl_2 (4:1), 0 °C to r.t., 70%; (c) $CuBr_2$, DBU, HMTA, CH_2Cl_2, 90%; (d) K_2CO_3, MeOH–H_2O (4:1), 89%; (e) (i) **11**, Et_3N, 2,4,6-trichlorobenzoyl chloride; (ii) **12**, Et_3N, DMAP, CH_2Cl_2, 0 °C to r.t., 92%; (f) (i) NCS, DMF, 0 °C to r.t.; (ii) *i*-Pr_2NEt, DMF, r.t.; (g) (i) K_2CO_3, MeOH, reflux; (ii) MeI, r.t., 72% (2 steps); (h) $LiBH_4$, MeOH, THF, 64%; (i) Dess–Martin periodinane, CH_2Cl_2, 89%; (j) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –10 °C, 82%.

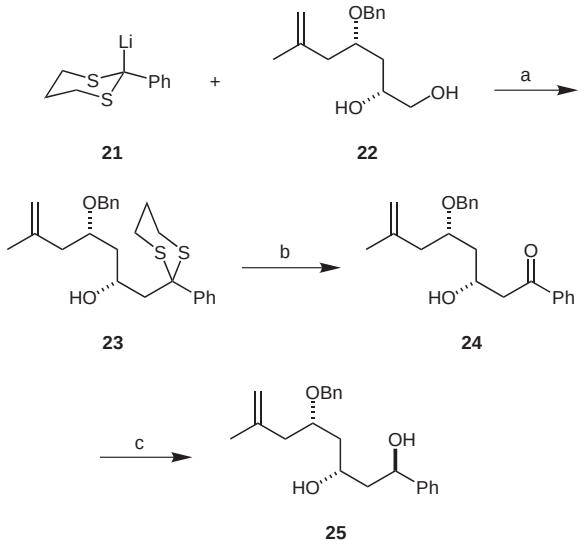
the pure *Z*-isomer **20**. The choice of a trityl group was critical here, as the more activated benzoate protecting group is prone to elimination and alkene isomerization upon oxidation to the aldehyde. Desilylation and treatment with Dess–Martin periodinane[28] produced the unstable β,γ-unsaturated aldehyde,[29] which was converted to the *E*-alkene under Schlosser conditions.[30] Acidic detritylation of the inseparable mixture of isomers then gave the desired alcohol **4**.[31] The Schlosser olefination, while poorly selective in this case, was the only procedure of many that ultimately afforded the requisite diene.[32] We exhaustively explored alternatives in which the disubstituted olefin was installed before the trisubstituted one. While this did allow for a more selective introduction of the *E* geometry, subsequent products in the pathway were quite volatile and provided lower overall yields.

With all three of our initial targets in hand, we set out to study the union of these fragments to form the hennoxazoles. Since our goal was to introduce the C22 stereocenter as late as possible to maintain flexibility, we explored the opening of epoxide **2** using 2-phenyl-1,3-dithiane (**21**)[33] as a model for the bisoxazole dithiane **3** (Scheme 5). One-pot epoxidation of **22** and ring opening by **21**[34] led to dithiane alcohol **23** in good overall yield.



Scheme 4 Synthesis of skipped diene **4**. *Reagents and conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, 95%; (b) $LiBH_4$, MeOH, Et_2O, 0 °C to r.t., 92–98%; (c) Dess–Martin periodinane, CH_2Cl_2, 92%; (d) **18** (1.2 equiv), 80% (*Z*/*E* = 11:1), Et_2O–THF (6:1), –78 °C; (e) DIBAL, toluene, 0 °C (81%); (f) TrCl, Et_3N, DMAP, CH_2Cl_2, 90%; (g) TBAF, THF; (h) Dess–Martin periodinane, CH_2Cl_2, 90% (2 steps); (i) (i) Ph_3PCHMe, LiBr, MeLi, r.t. to –78 °C; (ii) **20**, –30 °C; (iii) MeLi, –30 °C; (iv) *t*-BuOK, *t*-BuOH, Et_2O–THF (1:2), 62%, (*E*/*Z* = 5:4); (j) Dowex 50WX8 H^+ resin, MeOH, 61%

Subsequent removal of the dithiane[35] gave ketone **24**, which was suitable for either directed or chelation-controlled reduction. The latter was required for the natural product, and exposure to Prasad's conditions smoothly afforded the desired diol **25**.[36]



Scheme 5 Model study for coupling of bisoxazole **3** and diol **8**. *Reagents and conditions*: (a) (i) **22**, tosylimidazole, 0 °C to r.t.; (ii) NaH, 0 °C to r.t.; (iii) **21**, THF, –40 °C to –10 °C, 85%; (b) $AgNO_3$, NCS, MeCN–H_2O (4:1), 69%; (c) $Et_2B(OMe)$, $NaBH_4$, THF–MeOH (4:1), –78 °C, 82%

With a method established to install the final stereocenter, we turned our attention to the union of **2** and **3**. Unfortunately, all attempts to use dithiane **3** were unsuccessful, for the compound decomposed almost immediately under basic conditions. A monooxazole dithiane model[37] (Figure 3) survived long enough for deuteration of the dithiane, indicating that the high base-sensitivity of **3** may be a property specific to bisoxazoles. This conclusion was supported by subsequent deprotonation studies of Williams[38] and Smith[8] indicating the acidity of the C13 position. Their results suggest that a method of protecting the C13 site from deprotonation must be used for successful completion of this route, but Liu and Panek have shown that excess *t*-BuLi can deprotonate a polyoxazole dithiane with the appropriate selectivity.[39] Despite this challenging step, the route provides useful techniques for the synthesis of cyclopentylidene ketals, bisoxazoles, and β,γ-unsaturated aldehydes that should be more generally applicable.

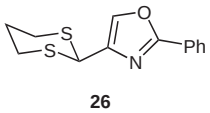


Figure 3

Acknowledgment

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References and Notes

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(2) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173.
(3) Higa, T.; Tanaka, J.-I.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227.
(4) For a review on oxazole-containing natural products, see: Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995.
(5) (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.
(6) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924.
(7) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415.
(8) Smith, T. E.; Balskus, E. P. *Heterocycles* **2002**, *57*, 1219.
(9) (a) Cheng, Z.; Hamada, Y.; Shioiri, T. *Synlett* **1997**, 109. (b) Shioiri, T.; McFarlane, N.; Hamada, Y. *Heterocycles* **1998**, *47*, 73. (c) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169. (d) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *51*, 6311.
(10) Hanessian, S. H.; Ugolini, A.; Dubé, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.

(11) (a) This method improves upon preceding methods for isopentylidene synthesis, for it requires only commercially available reagents. (b) **Procedure for Isopentylidene Synthesis**: To a 1-L flask under N_2 were added the *S*-enantiomer of triol **5** (21.01 g, 0.1980 mol), 3-pentanone (80 mL, 0.79 mol), trimethyl orthoformate (33 mL, 0.30 mol), *p*-TsOH (0.44 g, 0.023 mol), anhyd MeOH (75 mL), and distilled CH_2Cl_2 (150 mL). The mixture was heated to reflux and stirred for 15 h. Et_3N (1.8 mL, 0.013 mol) was added, and the mixture was stirred for 30 min. H_2O (100 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $NaSO_4$, filtered, and concentrated to a clear, yellow-brown liquid. Flash chromatography (20% EtOAc–hexanes) yielded the 1,2-isopentylidene-protected **5** as a clear, yellow-tinged liquid (29 g, 85%). IR: 3510, 2950, 1460, 1170, 1080 cm^{-1}. ^1H NMR (300 MHz): δ = 0.87–0.93 (m, 6 H), 1.59–1.69 (m, 4 H), 1.79–1.85 (m, 2 H), 2.26 (t, *J* = 5.0 Hz, 1 H), 3.54 (t, *J* = 8.0 Hz, 1 H), 3.81 (dd, *J* = 6.0, 12.0 Hz, 2 H), 4.10 (dd, *J* = 6.0, 7.9 Hz, 1 H), 4.25 (m, 1 H).

(12) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

(13) (a) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827.

(14) Spectral data for diol **8**: ^1H NMR (300 MHz): δ = 1.50 (ddd, *J* = 2.9, 7.8, 14.6 Hz, 1 H), 1.62–1.76 (m, 4 H), 2.19 (dd, *J* = 7.6, 13.8 Hz, 1 H), 2.47 (dd, *J* = 5.5, 13.7 Hz, 1 H), 2.85 (s, 2 H), 3.40 (dd, *J* = 6.8, 11.2 Hz, 1 H), 3.56 (dd, *J* = 3.3, 11.2 Hz, 1 H), 3.78 (s, 3 H), 3.82–3.90 (m, 1 H), 3.91–4.02 (m, 1 H), 4.42 (d, *J* = 11.0 Hz, 1 H), 4.56 (d, *J* = 11.0 Hz, 1 H), 4.76 (s, 1 H), 4.81 (s, 1 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 7.26 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 22.8, 36.2, 42.1, 55.2, 66.9, 69.0, 70.9, 74.5, 113.3, 113.9, 129.5, 130.1, 142.2, 159.3.

(15) For preparation of a related bisoxazole, see: Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971.

(16) (a) Szczepankiewicz, B. *Ph.D. Thesis*; University of California at Berkeley: USA, **1995**. (b) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6029.

(17) Attempts with serine ethyl ester afforded a higher yield for the amidation (80%) and comparable yields for the first oxazole synthesis; however, as the ethyl ester was less readily accessible, the methyl ester was used.

(18) **General Procedure for Oxazoline Synthesis**: To a dry 100-mL flask under N_2 was added a solution of the amide **10** (1.00 g, 3.39 mmol) in anhyd MeCN–CH_2Cl_2 (4:1, 15 mL), Ph_3P (1.33 g, 5.08 mmol), and DIPEA (0.94 mL, 5.47 mmol). After the mixture was cooled in an ice-bath for 90 min, CCl_4 (0.50 mL, 5.16 mmol) was added slowly. After 14 min, the mixture was allowed to warm to r.t. and stirred for 5.25 h. The mixture was cooled in an ice bath. EtOAc (30 mL) and sat. aq $NaHCO_3$ (9 mL) were added, and after 10 min, the biphasic mixture was diluted with H_2O (21 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL); the combined organic layers were washed with brine (1 × 20 mL), dried over $NaSO_4$, filtered, and concentrated to a yellow solid. Flash chromatography (25–50% EtOAc gradient in hexanes) yielded the water-sensitive oxazoline as a clear yellow oil (0.66 g, 70%). ^1H NMR (300 MHz): δ = 1.98 (m, 2 H), 2.47 (m, 2 H), 3.54 (t, *J* = 6.1 Hz, 2 H), 3.46 (dd, *J* = 8.8, 10.6 Hz, 1 H), 3.79 (s, 3 H), 4.46–4.50 (m, 3 H), 4.66–4.69 (m, 1 H), 7.27–7.36 (m, 5 H).

(19) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.-C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494.

(20) (a) Shapiro, R. *J. Org. Chem.* **1993**, *58*, 5759. (b) For best results we suggest purifying the amine **12** shortly before amide synthesis, as yields for the bisoxazole cyclization dropped by as much as 30% in other cases.

(21) The reduction of the bisoxazole was a sensitive reaction; during a repetition on larger scale, yields dropped to 30% because of competitive decomposition.

(22) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469.

(23) Spectral data for dithiane **3**: ^1H NMR (300 MHz): δ = 2.03–2.18 (m, 4 H), 2.94–3.00 (m, 6 H), 3.56 (t, *J* = 6.1 Hz, 2 H), 4.50 (s, 2 H), 5.18 (s, 1 H), 7.26–7.32 (m, 5 H), 7.74 (s, 1 H), 8.16 (s, 1 H). ^{13}C NMR (100 MHz): δ = 24.9, 25.1, 26.8, 30.3, 41.4, 68.7, 72.8, 127.5, 127.5, 128.2, 130.0, 135.7, 138.1, 138.3, 140.5, 155.2, 165.7.

(24) We tested the enantiomeric purity of aldehyde **17**'s enantiomeric purity by reducing a sample to the alcohol and comparing its rotation to the alcohol produced by lithium borohydride reduction of ester **16**. We observed only 1.5% racemization, which we judged acceptable. See: Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(25) (a) Joe, D. *Ph.D. Thesis*; University of California at Berkeley: USA, **1994**. (b) The phosphonate is prepared by Arbuzov reaction between methyl 2-bromopropionate and trimethyl phosphite. This method is capricious and highly sensitive to the purity of the starting materials. (c) The lithium enolate was deprotonated with *n*-BuLi (1.01 equiv) in Et_2O (0.125 M) at 0 °C to r.t.

(26) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) The unusual *Z* selectivity is only maintained for the olefination reagent with methyl ester and methyl phosphonate. (c) The stereochemistry of the two isomers of **19** was corroborated by chemical shift calculations: Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons: New York, **1991**, 215.

(27) Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.

(28) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(29) (a) The β,γ-unsaturated aldehyde could survive at room temperature for over a day without appreciable decomposition. In contrast, the benzoate-protected analogue would decompose within hours, and it could only be synthesized in low yield (33–56%). (b) Spectral data for the (*S*)-β,γ-unsaturated aldehyde: $[\alpha]_D^{20}$ +135 (*c* = 0.54, $CHCl_3$). ^1H NMR (300 MHz): δ = 1.05 (d, *J* = 6.9 Hz, 3 H), 1.94 (d, *J* = 1.2 Hz, 3 H), 2.95–3.00 (m, 1 H), 3.58 (d, *J* = 10.6 Hz, 1 H), 3.68 (d, *J* = 10.6 Hz, 1 H), 5.07 (d, *J* = 9.5 Hz, 1 H), 7.21–7.48 (m, 15 H), 9.38 (d, *J* = 1.3 Hz, 1 H). ^{13}C NMR (100 MHz): δ = 14.1, 22.3, 46.0, 62.7, 86.7, 123.8, 127.0, 127.7, 128.6, 137.8, 143.9, 201.2.

(30) (a) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821. (b) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R. Jr.; Whittle, R. R.; Olofson, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 7664.

(31) (a) Spectral data for diene **4**: ^1H NMR (300 MHz): δ = 0.99 (t, *J* = 5.1 Hz, 3 H), 1.61–1.68 (m, 3 H), 1.76–1.78 (m, 3 H), 3.08 (m, 1 H), 3.42–3.50 (m, 1 H), 3.96–4.18 (m, 2 H), 5.10–5.38 (m, 3 H). (b) Spectral data for *ent*-(*S*)-**20**: IR: 3022, 2947, 2855, 2307, 1112, 1085, 702 cm^{-1}. ^1H NMR (300 MHz): δ = 0.94 (d, *J* = 6.7 Hz, 3 H), 1.02 (s, 9 H), 1.89 (d, *J* = 1.1 Hz, 3 H), 2.40–2.50 (m, 1 H), 3.38 (dd, *J* = 1.7, 9.5 Hz, 2 H), 3.48 (d, *J* = 10.4 Hz, 1 H), 3.75 (d, *J* = 10.4 Hz, 1 H), 5.10 (d, *J* = 9.5 Hz, 1 H), 7.24–7.63 (m, 25 H). ^{13}C NMR (100 MHz): δ = 17.5, 19.1, 22.0, 26.7, 34.9, 62.8, 68.5, 86.4, 126.7, 127.4, 127.6, 128.6, 129.3, 131.1, 133.0, 133.8, 133.8, 135.5, 135.5, 144.3.

(32) A test reaction conducted with the aldehyde derived from *ent*-**20** and tetraethylphosphonium bromide did favor the *E*-olefin (*E*/*Z* = 4.8:1), but in unacceptably low yield (9%).
(33) For the synthesis of 2-phenyl-1,3-dithiane, see: Roberts, R. M.; Cheng, C.-C. *J. Org. Chem.* **1958**, *23*, 983.
(34) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122; and supplementary material.
(35) (a) Corey, E. J.; Erickson, B. J. *J. Org. Chem.* **1971**, *36*, 3553. (b) Trost, B. M.; Grese, T. A. *J. Org. Chem.* **1992**, *57*, 686.
(36) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(37) The model **26** was prepared from racemic *N*-benzoyl serine methyl ester by methods analogous to those used for the synthesis of oxazole **11** and dithiane **3**.
(38) Williams, D. R.; Brooks, D. A.; Meyer, K. A. *Tetrahedron Lett.* **1998**, *39*, 8023.
(39) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6147.