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Diastereoselective Total Synthesis of Both Enantiomers of Epolactaene

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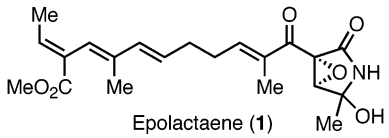
A stereocontrolled total synthesis of both the (+)- and (−)-epolactaene ((+)- and (−)-**1**) enantiomers from tetrahydropyran-2-ol is described. The following reactions in this synthesis are particularly noteworthy: (1) the stereoselective construction of the conjugated (*E*,*E*,*E*)-triene by a combination of kinetic deprotonation and thermodynamic equilibration, (2) the *E*-selective Knoevenagel condensation of *β*-ketonitrile **33** with a chiral 2-alkoxyaldehyde, (3) a diastereoselective epoxidation achieved using a bulky nucleophile (TrOOLi) and an appropriate protecting group, (4) the mild hydrolysis of an α-epoxy nitrile by silica gel on TLC facilitated by hydroxyl-mediated, intramolecular assistance.

Introduction

Epolactaene (**1**) is a microbial metabolite isolated by Kakeya, Osada, et al. from the fungal strain *Penicillium* sp. BM 1689-P.[1] As it is effective in promoting neurite



Epolactaene (**1**)

outgrowth and arresting the cell cycle at the G1 phase in a human neuroblastoma cell line, it is regarded as a potential treatment for various neurodegenerative diseases such as dementia.[2] Recently, epolactaene was found to inhibit the activities of mammalian DNA polymerases and human DNA topoisomerase II.[3] Structurally, epolactaene contains a labile (*E*,*E*,*E*)-triene and a novel 3-alkenoyl-3,4-epoxy-2-pyrrolidinone moiety. The 3-alkenoyl-2-pyrrolidinone group has been found in several natural products including pramanici,[4] L-755,807,[5] PI-091,[6] and fusarin C.[7] Because of its highly unusual structure and interesting biological properties and the scarcity of natural material, epolactaene has been an attractive target for organic chemists, and several research groups have undertaken its total synthesis. The first total syntheses of **1**, published by our[8] and Kogen's[9] laboratories in 1998, established its absolute stereochemistry to be 13*R*,14*R*. Kobayashi et al. also described a synthesis in 1999.[10]

Our Previous Synthesis of Epolactaene

Epolactaene contains an epoxylactam and a conjugated triene, both of which are thought to be labile, as the epoxy group of the former is activated by two adjacent electron-withdrawing groups, while the latter can be decomposed by acid, base, light, and oxidizing conditions. We planned to construct the triene first, and then to assemble the epoxylactam rapidly under mild reaction conditions. As the absolute stereochemistry was initially unknown, our synthetic route should provide easy access to both enantiomers. We succeeded in achieving these goals, and in determining the absolute stereochemistry, the key steps of our synthesis being summarized in Scheme 1. Tetrahydropyran-2-ol (**2**) was converted to (*E*,*E*)-dienecarboxylic acid derivative **3** stereoselectively by Wittig and Horner−Emmons reactions. After aldol reaction of ester **3** with acetaldehyde to afford (*E*,*E*)-diene derivative **4**, dehydration and isomerization reactions afforded conju-

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(1) Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 733.
(2) (a) Kakeya, H.; Onozawa, C.; Sato, M.; Arai, K.; Osada, H. *J. Med. Chem.* **1997**, *40*, 391. (b) Vantini, G,; Skaper, S. D. *Pharmacol. Res.* **1992**, *26*, 1. (c) Dicicco-Bloom, E.; Friedman, W. J.; Black, I. B. *Neuron* **1993**, *11*, 1101.
(3) Mizushima, Y.; Kobayashi, S.; Kuramochi, K.; Nagata, S.; Sugawara, F.; Sakaguchi, K. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 784.
(4) Schwartz, R. E.; Helms, G. L.; Bolessa, E. A.; Wilson, K. E.; Giacobbe, R. A.; Tkacz, J. S.; Bills, G. F.; Liesch, J. M.; Zink, D. L.; Curotto, J. E.; Pramanik, B.; Onishi, J. C. *Tetrahedron* **1994**, *50*, 1675.
(5) Lam, Y. K. T.; Hensens, O. D.; Ransom, R.; Giacobbe, R. A.; Polishook, J.; Zink, D. *Tetrahedron* **1996**, *52*, 1481.
(6) Kawashima, A.; Yoshimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. (Heisei). Jpn. Kokai Tokkyo Koho JP 02062859 A2 19900302, 1990.
(7) Eilbert, F.; Thines, E.; Arendholz, W. R.; Sterner, O.; Anke, H. *J. Antibiot.* **1997**, *50*, 443.
(8) Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998**, 313.
(9) Marumoto, S.; Kogen. H.; Naruto, S. *J. Org. Chem.* **1998**, *63*, 2068. *Tetrahedron* **1999**, *55*, 7129, 7145.
(10) Kuramochi, K.; Nagata, S.; Itaya, H.; Takano, K.; Kobayashi S. *Tetrahedron Lett.* **1999**, *40*, 7371.

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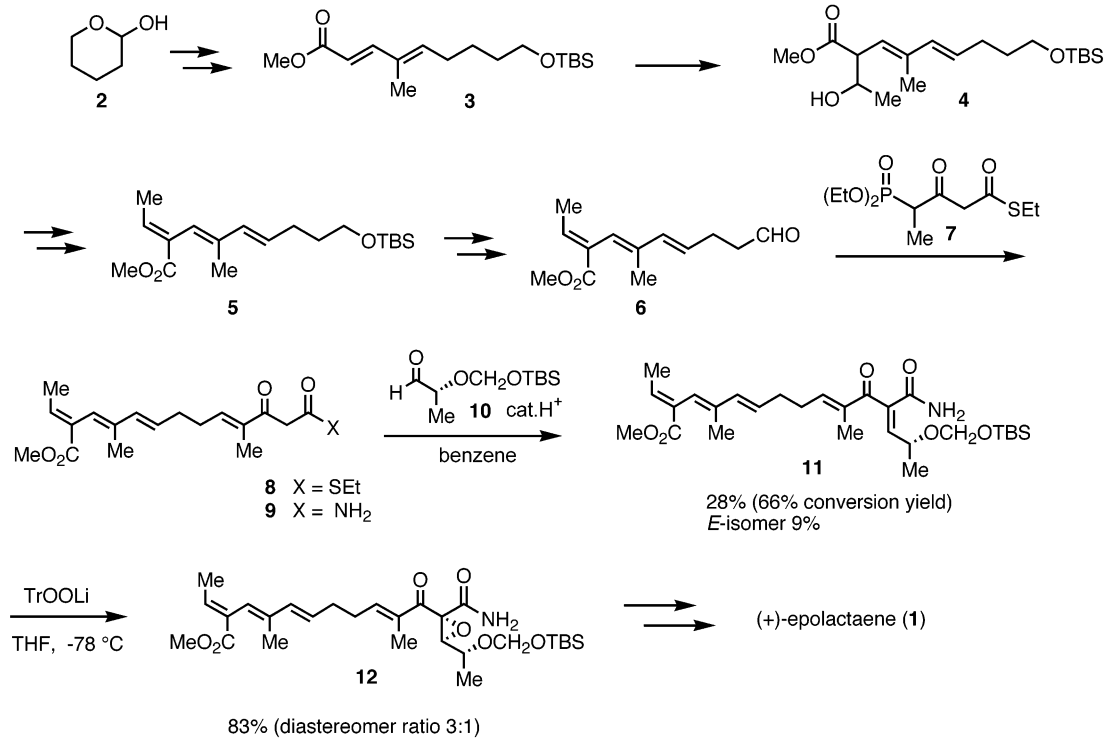
SCHEME 1. The First Total Synthesis of (+)-1



gated (*E*,*E*,*E*)-triene **5**, which was converted to triene aldehyde **6**. Horner−Emmons reaction of the newly developed *β*-ketothioester diethyl phosphonate derivative **7** and **6** proceeded smoothly to afford *γ*,*δ*-unsaturated *β*-ketothioester **8**. After transformation of the thioester to amide **9**, Knoevenagel condensation[11] with (*R*)-2-(*tert*-butyldimethylsiloxymethoxy)propanal (**10**), which was readily prepared from (*R*)-methyl lactate, afforded α,*β*-unsaturated amide **11**. Epoxidation of **11** gave epoxide **12**. Deprotection of the protecting group, followed by the oxidation, afforded (+)-**1** for the first time.

Thus, the first total synthesis of epolactaene had been accomplished, and its absolute stereochemistry determined.[8] However, two steps had proved unsatisfactory in terms of stereoselectivity and/or yield: One was the Knoevenagel condensation between *β*-ketoamide **9** and the chiral alkoxyaldehyde **10**, which afforded addition product **11** in low yield, and with low *E*/*Z*-selectivity. The other was the epoxidation reaction of **11** to give epoxide **12**, for which diastereoselectivity was low (ca. 3:1). For epolactaene and various analogues to be prepared in quantity, these two steps needed to be improved. In this paper, we describe the optimization of these steps, as well as full details of the stereocontrolled total synthesis of (+)-epolactaene by the application of these modifications.

Model Studies

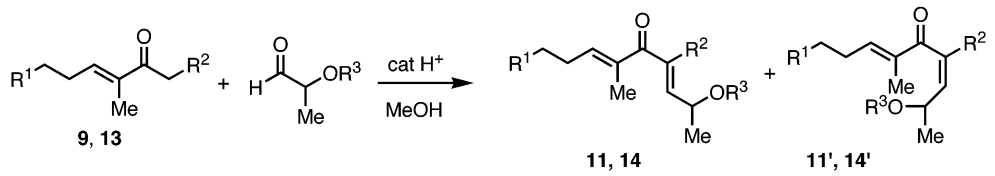
Because of the problems encountered in the Knoevenagel condensation of *β*-ketoamide **9** outlined above, we examined the reaction conditions in detail and found that the desired *Z*-isomer **11** is kinetically favored, while the *E*-isomer is the thermodynamic product; neither an increase in catalyst loading nor an increase in reaction time increased the yield of the desired *Z*-isomer. Altering the hydroxyl protecting group of the aldehyde partner does not improve the yield: Knoevenagel condensation of ketoamide **9** with an aldehyde containing the more bulky triethylsilyl protecting group proceeds slower in reduced yield (Table 1, entry 2). We turned to the possibility of using other *β*-ketoamide synthetic equivalents such as *β*-ketoester, *β*-ketothioester, and *β*-ketonitrile. Initial model studies centered on the reaction of substrates having a phenyl group instead of the triene moiety, with an α-alkoxypropanal, in the presence of a catalytic amount of ethylenediammonium diacetate.[12] The results for model substrates **13a**−**c** are summarized in Table 1. *β*-Ketoester **13a** did not react, and neither possible condensation product was formed (entry 3). Though the reactions of *β*-ketothioester **13b** with 2-(*tert*-butyldimethylsiloxymethoxy)propanal and with 2-triethylsiloxypropanal both proceeded, the undesired *E*-isomers **14′a** and **14′b** were exclusively formed in 84% and 48% yield, respectively[13] (entries 4 and 5, for the determination of the stereochemistry of Knoevenagel adducts of **14′a** and **14′b** vide infra). The difference in yield for these two aldehydes is due to the bulkiness of their protecting groups. The smaller this is, the better the yield. The high *E*-selectivity is a result of the ready isomerization of *Z*-isomer to *E*-isomer. *β*-Ketonitrile **13c**, however, reacted smoothly with both 2-(*tert*-butyldimethylsiloxymethoxy)-propanal and 2-triethylsiloxypropanal in a much shorter time than did *β*-ketothioester, to give the desired *E*-

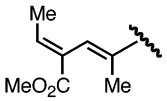
(11) For reviews, see: Jones, G. *Org. React. (N.Y.)* **1967**, *15*, 204. Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Editor-in-Chief; Pergamon Press: Oxford, 1991; Vol. 2, p 341.

(12) Tietze, L.-F.; Kiedrowski, G. v. *Tetrahedron Lett.* **1981**, 219; Tietze, L.-F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 1185.

(13) Hayashi, Y.; Miyamoto, Y.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 4079.

TABLE 1. Knoevenagel Reaction of 9 and 13



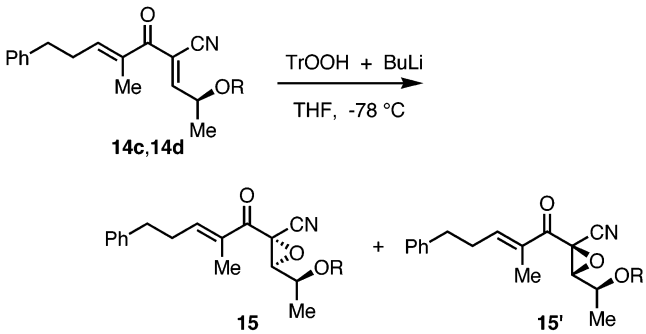
Entry	R^1	R^2	R^3	Time/h	Yield/%[a] 11,14	11', 14'
1		$CONH_2$ (**9**)	CH_2OSi-*t*-$BuMe_2$	10	28 (*Z*) (**11**)	9
2		$CONH_2$ (**9**)	$SiEt_3$	20	10 (*Z*)	0
3	Ph	$CO_2CH_2CH_2SiMe_3$ (**13a**)	CH_2OSi-*t*-$BuMe_2$	12	0	0
4	Ph	COSEt (**13b**)	CH_2OSi-*t*-$BuMe_2$	11	0	84 (*E*) (**14'a**)
5	Ph	COSEt (**13b**)	$SiEt_3$	19	0	48 (*E*) (**14'b**)
6	Ph	CN (**13c**)	CH_2OSi-*t*-$BuMe_2$	4	80 (*E*) (**14c**)	0
7	Ph	CN (**13c**)	$SiEt_3$	4	86 (*E*) (**14d**)	0

[a] Isolated yield. The character in parentheses indicates the geometry of the olefin.

adducts[14] **14c** and **14d** without formation of the *Z*-isomer (note the change in priority) in good yield (entries 6 and 7). *It is noteworthy that Knoevenagel condensations of β-ketonitrile* **13c** *and of β-ketothioester* **13b** *selectively afford the completely opposite stereoisomers.* This high *E*-selectivity for the cyano derivative can be attributed to the thermodynamic stability of this isomer, for which owing to the linear structure of the cyano group there is no increased steric repulsion in the *E*-olefin. This high *E*-selectivity with a *β*-ketonitrile is general to aldehydes: Not only the reaction with α-alkoxyaldehydes such as **10**, but also reactions with aromatic and aliphatic aldehydes such as benzaldehyde and isobutyraldehyde afford the *E* Knoevenagel condensation products stereoselectively.[15] The high chemical yields and short reaction time of the Knoevenagel reactions of the *β*-ketonitrile with aldehyde derivatives such as 2-(*tert*-butyldimethylsiloxymethoxy)propanal and 2-triethylsiloxypropanal, regardless of the relative bulkiness of their protecting groups, indicate that the *β*-ketonitrile is highly reactive as a Knoevenagel donor. This high reactivity of *β*-ketonitrile **13c** is due to the strong electron-withdrawing ability of the cyano group.

Next the stereoselectivity of the epoxidation was investigated (Table 2). Though the reaction of **14c** having the *tert*-butyldimethylsiloxymethyl protecting group with TrOOLi (Tr = Ph_3C) generated from TrOOH[16] and *n*-BuLi proceeded, the diastereoselectivity was very low (59:41). *On the other hand, nearly perfect stereoselection was realized in the reaction of* **14d**, *having the triethylsilyl protecting group with TrOOLi, in which the nucleophile attacks from the opposite face of the triethylsilyl protecting group at −78 °C, affording β-epoxide* **15d** *in 81% yield*

TABLE 2. Epoxidation Reaction of 14



entry	R	yield[a] (%)	**15**:**15′**
1	CH_2OSi-*t*-$BuMe_2$ (**14c**)	70	59:41
2	$SiEt_3$ (**14d**)	81	>99 (**15d**):<1

[a] Isolated yield.

(for determination of the stereochemistry vide infra). The bulky triethylsilyl protecting group is essential for this high selectivity because only low selectivity was observed in the reaction using the *tert*-butyldimethylsiloxymethyl-containing substrate. Chelation of the *tert*-butyldimethylsiloxymethoxy moiety with lithium ion would reduce the diastereoselectivity. The bulky nucleophile (TrOOLi) is also necessary for high selectivity, as lower diastereoselectivity (5:1) was observed when the less bulky *t*-BuOOLi was employed.

The remaining conceivable difficulty inherited with this *β*-ketonitrile methodology is that the cyano group must be hydrolyzed to an amide[17] under reaction conditions mild enough to be compatible with the conjugated triene. However, we happened to find a neat solution to

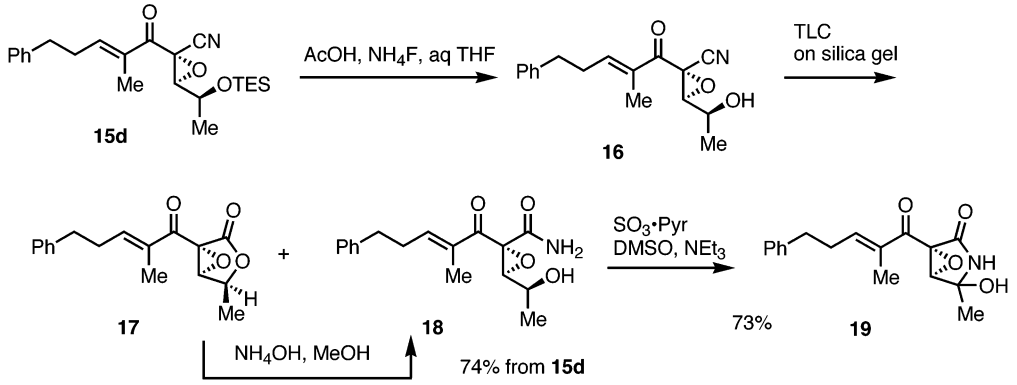
(14) Because of the instability of the condensation products, rough purification was performed by rapid column chromatography on florisil gel.

(15) The Knoevenagel reaction of *β*-ketonitrile **13c** with benzaldehyde and isobutyraldehyde afforded *E*-olefins selectively in 89% and 95% yields, respectively.

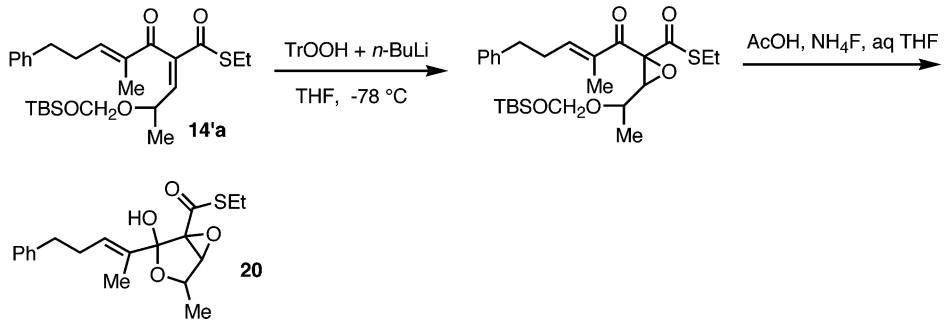
(16) Bissing, D. E.; Matuszak, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1964**, *86*, 3824.

(17) $RuH_2(PPh_3)_4$-mediated hydration of nitriles has been reported to proceed under neutral conditions at 120 °C, but our nitrile **16** was decomposed under the literature conditions. Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Am. Chem. Soc.* **1992**, *57*, 2521 and references therein.

SCHEME 2. Model Synthesis of the Epoxylactam Moiety 19 of Epolactaene



SCHEME 3. Determination of the Geometry of 14′a



this problem. During purification of alcohol **16** by thin-layer chromatography (TLC) on silica gel after removal of the TES protecting group, hydrolysis of the nitrile occurred via intramolecular hydroxy group assistance, affording epoxylactone **17** and epoxyamide **18** (Scheme 2). The former was successfully transformed to the latter by treatment with NH_4OH in MeOH at 0 °C for 30 min to give **18** in 74% yield over three steps from **15d**. Treatment of nitrile **16** with silica gel on TLC is crucial for this transformation: Stirring the nitrile **16** in several solvents in the presence of silica gel does not transform it to the hydroxy amide **18**. Other acidic conditions such as *p*-TsOH in MeOH, acetic acid, and trifluoroacetic acid are ineffective, generating several byproducts. Oxidation of **18** with SO_3•pyridine,[18] DMSO, and NEt_3 proceeded well, affording 3-alkenoyl-3,4-epoxy-2-pyrrolidinone **19** in 73% yield.

Assignment of Stereochemistry

The stereochemistry of Knoevenagel condensation products **14′a** and **14d** was determined as follows: As **14′a** could be converted to epoxyhydrofuran **20**,[19] by epoxidation and deprotection (Scheme 3), the geometry of **14′a** was determined to be *E*. On the other hand, as epoxylactone **17** was obtained from **14d** as shown in Scheme 2, the geometry of olefin **14d** was assigned to be *E* (note the change of priority).

The stereochemistry of epoxide **15d** was determined by an NOE study of the epoxylactone **17**, the other diastereomer of which, **17′**, had already been obtained in our previous synthesis of epolactaene.[8] An NOE

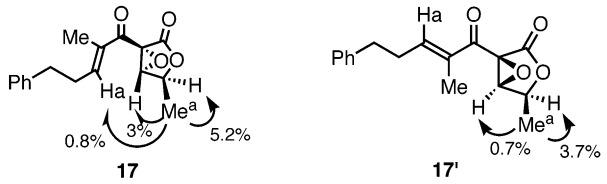


FIGURE 1. NOEs observed for lactones **17** and **17′**.

between Me^a and Ha was observed for **17**, but not detected for isomer **17′**. This establishes the stereochemistry of **17** and **17′** to be as depicted in Figure 1.

Total Synthesis of Epolactaene by the New Method

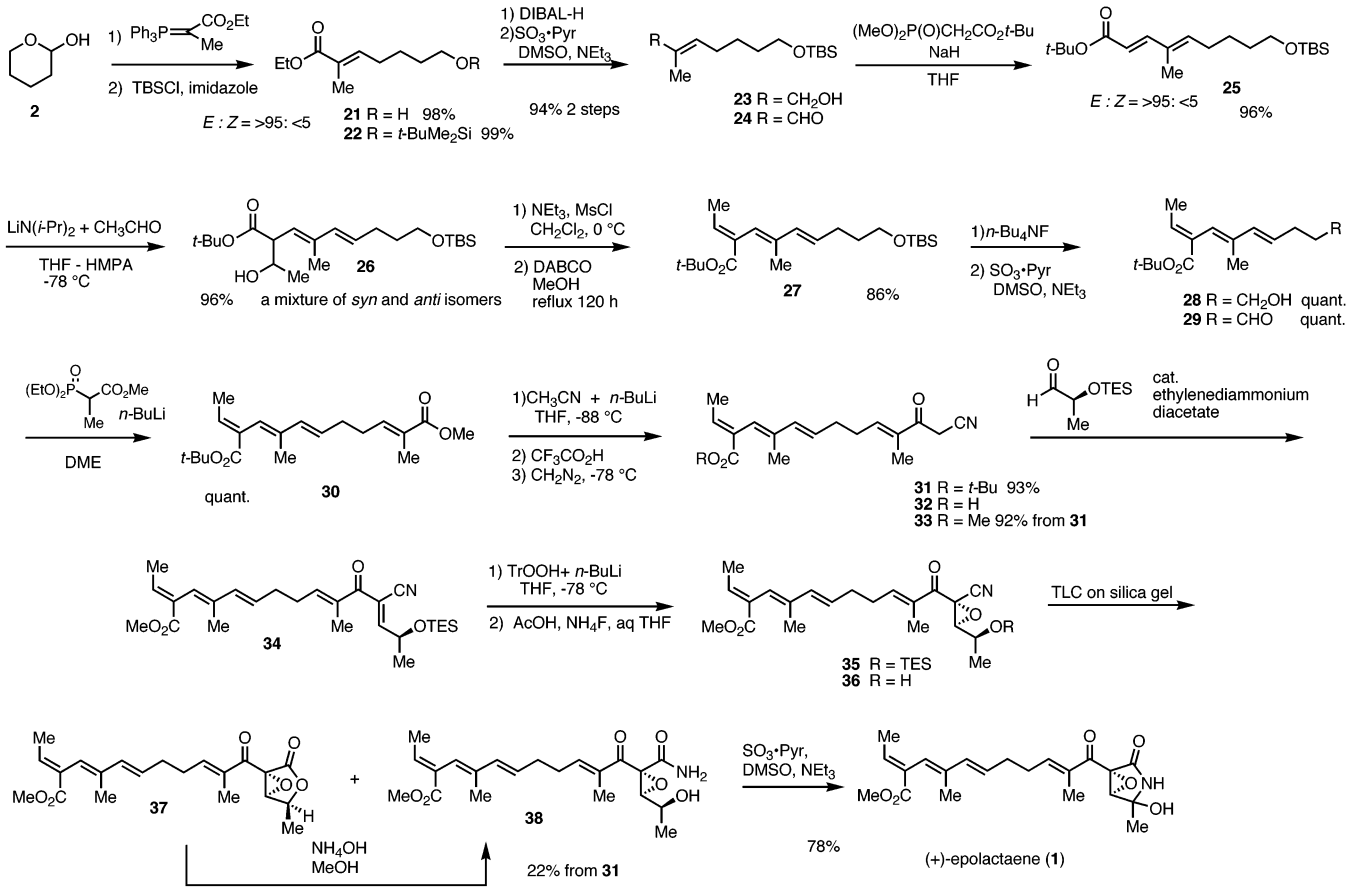
Having established an improved synthetic route to the 3-alkenoyl-3,4-epoxy-2-pyrrolidinone, this methodology was next applied to the total synthesis of epolactaene. As the difference between this synthetic route and the previous one is in the construction of the epoxylactam, synthetic procedures for the triene part are essentially the same, with only a few minor modifications. That is, methyl 9-(*tert*-butyldimethylsiloxy)-2-ethylidene-4-methylnona-3,5-dienoate (**5**) was the key triene intermediate in our first synthesis,[8] while the corresponding *tert*-butyl ester derivative **27** is required for the new route to discriminate between the two ester groups in the reaction of advanced intermediate **30** with $LiCH_2CN$ (vide infra, Scheme 4).

Wittig coupling of **2** with (ethoxycarbonylethylidene)-triphenylphosphorane in toluene at 90 °C for 1 h afforded *E*-unsaturated ester **21** stereoselectively (*E*:*Z* = >95:<5) in 98% yield, the hydroxy group of which was protected by treatment with *tert*-butyldimethylsilyl chloride (TB-

(18) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(19) The stereochemistry of epoxyhydrofuran **20** was not determined.

SCHEME 4



SCl) and imidazole in CH_2Cl_2 to give TBS ether **22** in 99% yield. Conversion of **22** to *tert*-butyl (*E*,*E*)-2,4-nonadienoate **25** was accomplished stereoselectively by the following sequence: (1) reduction of ester **22** to allylic alcohol **23** by diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 from −78 to 0 °C; (2) oxidation of the allylic alcohol **23** to aldehyde **24** by SO_3·pyridine,[18] DMSO, and NEt_3 in CH_2Cl_2, 94% yield over two steps;[20] (3) Horner−Emmons reaction of **24** with *tert*-butyl dimethylphosphonoacetate and NaH in THF at 0 °C to afford **25** in 96% yield. Aldol condensation of the lithium enolate generated from **25** and lithium diisopropylamide (LDA) in THF−HMPA at −78 °C with acetaldehyde at −78 °C for 3 h gave *syn*- and *anti*-aldols **26** in 96% yield in a 1:1.7 ratio, which could be separated by column chromatography but were used as a mixture in the next step. The diene moiety of these aldol isomers has the *E*,*E*-geometry, with no other isomers being formed. This high *E*,*E*-selectivity can be attributed to the selective, kinetic deprotonation of proton Ha from the most stable conformation, in which repulsion between the methyl and R groups is minimized, as shown in Figure 2.

The mixture of *syn*- and *anti*-aldols **26** was converted to *tert*-butyl (3*E*,5*E*)-2-[(*E*)-ethylidene]-4-methyl-3,5-nonadienoate derivative **27** as follows: The aldols **26** were transformed into their mesylates by reaction with methanesulfonyl chloride, NEt_3, and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2. Elimination of methanesulfonic acid from the crude mesylates and isomerization using 1,4-diazabicyclo[2.2.2]-octane (DABCO)[21] in MeOH at reflux for 120 h[22] afforded a 15:1 mixture of (*E*)- and (*Z*)-ethylidene derivatives **27** in 86% yield. The following points about this transformation are noteworthy: (1) The (*E*)-ethylidene derivative **27** was stereoselectively formed from the *syn*-aldol at rt by treatment with DABCO, while a mixture of *Z*- and *E*-isomers was obtained from the *anti*-aldol. (2) Isomerization of the *Z*-isomer to the *E*-isomer **27** proceeded gradually in MeOH under reflux in the presence of DABCO.

Since stereoselective preparation of diene **27** had been achieved, the construction of the 3-alkenoyl-3,4-epoxy-2-pyrrolidinone was next examined. Deprotection of the silyl ether using *n*-Bu_4NF in THF at rt for 2 h afforded alcohol **28** quantitatively, and then SO_3·pyridine[18] oxidation gave aldehyde **29**, also quantitatively. The Horner−Emmons reaction of **29** with methyl 2-(diethylphosphono)-

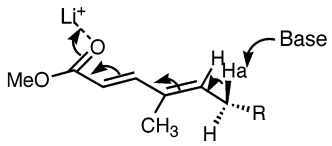


FIGURE 2. Kinetic deprotonation of Ha with LDA.

(20) Griffith−Ley oxidation with 4-methylmorpholine *N*-oxide and a catalytic amount of tetrapropylammonium perruthenate in the presence of molecular sieves 4A was employed in our previous synthesis of epolactaene.[8] Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(21) DABCO is more effective than DBU, which was used in our previous synthesis of epolactaene. [8]

(22) The isomerization of *tert*-butyl ester (*Z*)-**27** was slower than that of the corresponding methyl ester, which was used in our previous synthesis of epolactaene.[8]

propanate and *n*-BuLi in DME[23] at rt afforded *E*-α,*β*-unsaturated ester **30** quantitatively with high *E*-selectivity. The reaction of methyl ester **30** with $LiCH_2CN$ (2 equiv) proceeded in 1 min at −88 °C, affording *β*-ketonitrile **31** in 93% yield, while over-reaction at the *tert*-butyl ester moiety was observed at higher temperatures and longer reaction times. After cleavage of the *tert*-butyl ester with CF_3CO_2H, the resulting carboxylic acid **32** was reacted with diazomethane at −78 °C, affording methyl ester **33** in 92% yield over two steps. Low temperature is again a key to the success of this transformation, because a *β*-methoxy-α,*β*-unsaturated nitrile is formed at 0 °C.

The critical Knoevenagel condensation between *β*-ketonitrile **33** and (*S*)-2-triethylsiloxypropanal proceeded in the presence of a catalytic amount of ethylenediammonium diacetate, affording the addition product **34**. Owing to the instability of **34** and the next intermediate **35**, isolation was not performed until the purification of **38**. After short column chromatography on florisil gel, the crude material **34** was treated with TrOOLi at −78 °C, affording the epoxide **35**. The following three reactions, deprotection of the TES group with AcOH and NH_4F in aq THF, hydrolysis of the nitrile by silica gel on TLC, and ammonolysis of the lactone-formed **37** by NH_4OH in MeOH, were carried out to afford hydroxyamide **38** in 22% yield over five steps (average 74% per step) after purification on TLC. These five steps proceeded as efficiently as in the model series, generating the functionalized compound stereoselectively. The final oxidation could be achieved using SO_3·pyridine,[18] DMSO, and NEt_3 in CH_2Cl_2, affording (+)-**1** in 78% yield.

Though we had succeeded in developing an improved total synthesis of (+)-**1**, there remains the possibility of racemization having occurred at the chiral center. That is, the chiral 2-siloxypropanal may racemize during the Knoevenagel reaction, not only because it has an acidic α-hydrogen but also because an easily enolizable imine may readily be formed by reaction with ethylenediammonium diacetate.[24] The Knoevenagel adduct **34** may also racemize under the basic epoxidation conditions, because the allylic proton of **34** is likely to be acidic due to the neighboring vinylogous *β*-ketonitrile structure. However, the NMR spectra of the MTPA esters[25] of epoxides **36** prepared from optically active and racemic 2-triethylsiloxypropanal revealed that no racemization had in fact occurred under the present reaction conditions.

Synthetic (+)-**1** exhibited spectral data identical to those reported for the natural substance (^1H NMR, ^{13}C NMR, and mass spectroscopies), as well as a very similar optical rotation (synthetic epolactaene, $[\alpha]_D^{26}$ +31 (*c* = 0.12, MeOH); natural epolactaene, $[\alpha]_D^{26}$ +32 (*c* = 0.1, MeOH)[1]). In addition, synthetic (+)-**1** shows almost the same biological activity as natural (+)-**1** in SH-SY5Y cells. The enantiomer of epolactaene was also synthesized by the same route using (*R*)-2-triethylsiloxypropanal as the Knoevenagel condensation partner with *β*-ketonitrile **33**. Detailed biological studies on both enantiomers of epolactaene and several analogues are now under way, the results of which will be reported in due course.

In summary, both enantiomers of epolactaene have been synthesized in an enantio- and diastereoselective manner. This synthesis has several noteworthy features: (1) the stereoselective formation of a substituted conjugated (*E*,*E*,*E*)-triene, the diene unit of which was stereoselectively synthesized by kinetic deprotonation, with the final olefin being prepared selectively by thermodynamic equilibration, (2) the complementary stereoselective Knoevenagel reactions of *β*-ketonitriles and *β*-ketothioesters, which afforded opposite stereoisomers, (3) stereoselective epoxidation by a combination of a suitable protecting group and a bulky hydroperoxide, (4) the mild hydrolysis of a nitrile by silica gel during TLC involving intramolecular assistance by a hydroxyl group.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of the ^1H and ^{13}C NMR and IR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) A probable mechanism for the Knoevenagel reaction is as follows: an ammonium salt reacts with an aldehyde to afford an imine, which then reacts with a nucleophile. The isomerization of imine and enamine is a well-known process, which leads to the racemic imine. For the above reaction mechanism, see the reviews in ref 11.

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