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Dianion Equivalents Corresponding to the Polypropionate Domain of Epothilone B

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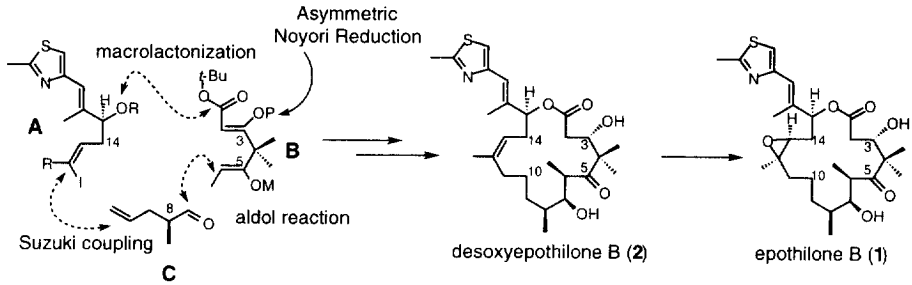
Abstract

A modified synthesis of the polypropionate portion of epothilone, which utilizes a novel, diastereoselective aldol reaction of (*S*)-2-methyl-4-pentenal (**4**) and the *Z*-enolate of the tricarbonyl species (**3**) is reported.

Keywords: epothilone B, aldol, polypropionate, methyl enol ether

In 1996 and 1997, this laboratory disclosed the first syntheses of the antimitotic agents epothilones A and B (**1**), respectively.[1,2] These stereocontrolled, although lengthy, ventures provided sufficient amounts of fully synthetic epothilones for *in vitro* cytoxicity and tubulin binding studies. Indeed, after due persistence, epothilone B could be amassed in amounts adequate for *in vivo* studies against xenografts of human tumors in nude mice. These studies suggested some potentially serious maximum tolerated dose (M.T.D) toxicity problems with the parent agent. However experiments with 12,13-desoxyepothilone B, **2**, proved to be rather promising. Though the *in vivo* and *in vitro* potency of **2** are significantly lower that those of **1**, the 12,13-desoxy system dramatically outperforms paclitaxel. Moreover, in drug resistant xenografts, compound **2** is clearly superior to paclitaxel.[3] These findings underscored the need for a synthesis of **2** capable of supporting a serious compound development effort. Toward this end, we considered a major departure from our original academic syntheses. The governing concepts are summarized below.



It was anticipated that the C1-C11 polypropionate domain could be assembled through a single defining aldol condensation of the C5-C6 *Z*-metalloenolate system **B** and readily available **C**. We would also require high selectivity in fashioning the requisite erythro (by *uk* addition) connectivity between the emerging

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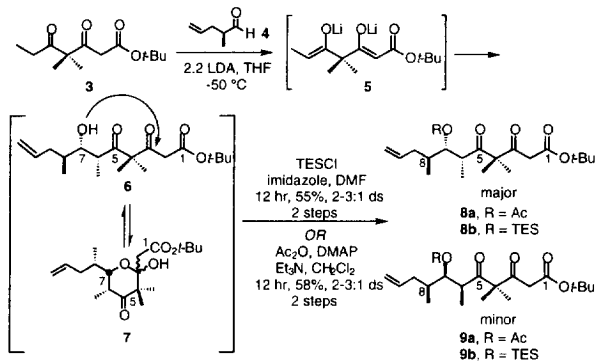
stereocenters at C6-C7 as well as the required anti relationship relative to the resident chirality at C8 (by *lk* diastereoface addition). Needless to say, provisions would be necessary to steer the required aldol condensation to C6 in preference to the more readily enolizable center at C2.

Three tactical approaches were pursued toward this latter end. Initially, the aldol reaction was performed directly between aldehyde **4** and the dianion derived from tricarbonyl **3** (Scheme 1) under the conditions shown. While C-C bond formation did occur at C6, the resultant C7 β-hydroxyl functionality tended to cyclize to the C-3 carbonyl group, thereby affording a complex mixture of lactol and hydroxy ketone products. Lactol formation could be reversed (see **7**→**6**) following treatment of the crude aldol product with TESCl/2,6-lutidine in DMF or with acetic anhydride. Under these conditions there was obtained an inseparable 4:1 mixture of desired **8** (**a** or **b**):**9** (**a** or **b**)[4] products. Further complicating matters was the fact that neither the acetate nor TES groups were sufficiently stable to service the rest of the synthesis. Unfortunately more durable blocking groups could not be introduced onto the C7 hydroxyl by trapping of **6** derived from **7**.

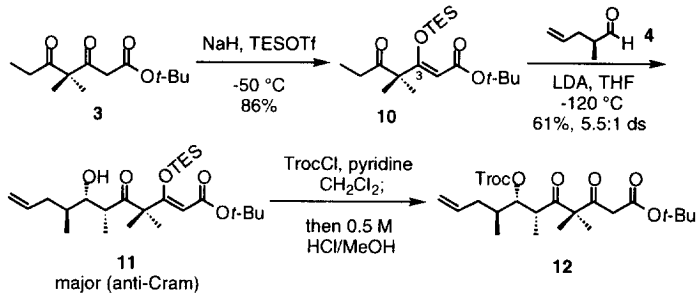
Scheme 1



To overcome the obstacles arising from lactolization, we sought to engage the C3 carbonyl group in the aldol nucleophile as an enol ether. In this way, unwanted cyclization would not occur, and the C7 hydroxyl group could be protected in a more durable fashion. As reported in our recent disclosure,[5] the triethylsilyl (TES) enol ether (**10**) (Scheme 2) can be readily generated from the tricarbonyl, **3**. The resultant enol ether did successfully undergo an aldol coupling with aldehyde **4**. Without the difficulties encountered by undesired hemiacetal formation, the C7 hydroxyl moiety could be readily protected as the trichloroethoxycarbonate ester (Troc). Happily, the aldol reaction between enol ether **10** and aldehyde **4** gave rise to a 1:5.5 mixture of C7-C8 *syn* and C7-C8 *anti* isomers. These diastereomers could be separated by flash column chromatography.[6]

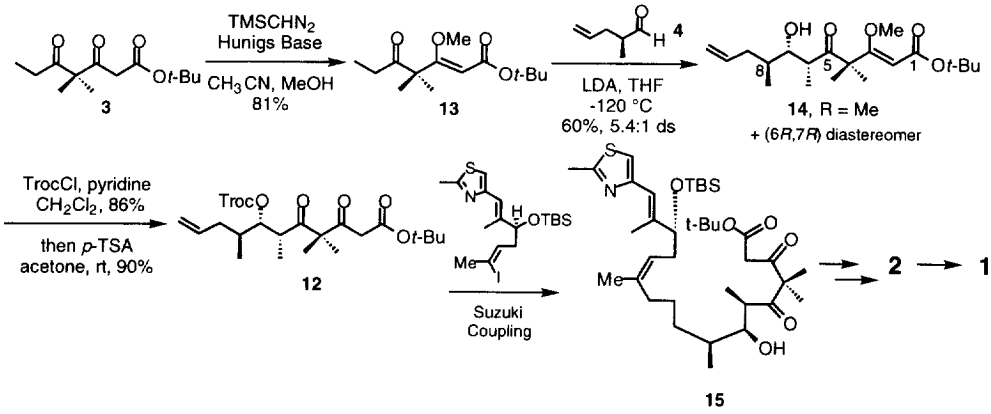
In attempted scaleups, the aldol reaction between **9a** and aldehyde **3** proved to be troublesome. The resultant C3 TES enol ether in **11** was prone to decomposition under the very basic conditions of the aldol reaction and was also quite sensitive to silica gel chromatography. While the TES enol ether was quite stable to LDA at -78 °C, complete enolate formation required much higher temperatures (-30 °C). Under these somewhat more forcing conditions, the TES enol ether was at risk to decomposition.

Scheme 2



Thus, we sought a different protecting group that would be stable to both silica gel chromatography and the basic aldol reaction conditions. We investigated the usefulness of a methyl enol ether linkage. We soon discovered that the requisite methyl enol ether, **13**,[7] could be readily prepared from trimethylsilyl diazomethane, $TMSCHN_2$, with Hunig's base in high yield and as a single olefin isomer (Scheme 3). Fortunately, the aldol reaction performed on the methyl enol ether also afforded the same diastereoselectivity as the TES enol ether. Likewise, the diastereomers (**14**[8] and its C8 epimer) obtained in the aldol reaction could be readily separated by flash column chromatography on silica gel. Subsequent reaction with trichloroethoxycarbonyl (Troc) chloride afforded the desired C7 protected compound which could be hydrolyzed cleanly and in high yield (*p*-toluenesulfonic acid (*p*-TSA), acetone, rt, 4-6 hrs) to afford the desired tricarbonyl structure **12,** in place for a *B*-alkyl Suzuki coupling.

Scheme 3



The latter steps in the synthesis employed previously described chemistry[5] to afford desoxyepothilone B (**2**) in amounts suitable for ongoing development needs. We note that the ratio of diastereofacial selectivity of the aldol step using the nucleophiles derived from the TES enol ether **10** and methyl enol ether **13** is consistently slightly higher than the ratio obtained when using dianion **5**. The slight erosion of selectivity in the latter case **5** is rationalized by the higher reactivity associated with the dianion nucleophile. Some fascinating effects of varying the remote substituents of the aldehyde on the diastereoselectivity observed in the reaction are described in the paper which follows.

Through use of the enol methyl ether route to the once problematic polypropionate domain of epothilone, we are now able to prepare 12,13-desoxyepothilone B (**2**), in quantities suitable for *in vivo* testing of efficacy and toxicity. This fully synthetic compound and analogues thereof also prepared by total synthesis are currently being developed with a view to clinical use.

Acknowledgments

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4 The stereochemistry of the diastereomeric products isolated in this reaction were confirmed to be those arising from incomplete relative face selectivity of the aldol reaction (Felkin:Anti-Felkin). Thus the stereochemistry was proven by comparing the ^{1}H NMR spectrum of the major diastereomer with a compound of known stereochemistry that had been independently synthesized.

5 Balog , A; Harris, C.; Savin, K. *Angew Chem Int Ed Engl*, , **1998**, 2675-2678.

6 A detailed study of the source of this exceptional relative facial selectivity observed with α-methyl aldehydes is reported in the following article.

7 Aoyama, T.; Terasawa, S.; Sudo, K.; Shiori, T. *Chem. Pharm. Bull.* **1984**, 32, 3759. Spectral data for **8b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (s, 1H), 3.88 (s, 3H), 2.45 (q, J = 7.33 Hz, 2H), 1.48 (s, 9H), 1.25 (s, 6H), 1.02 (t, J = 7.21 Hz, 3H).

8 The aldol reaction was carried out according to the following general procedure. The methyl enol ether, **8b** (1.0 g), and 100 mL of dry THF were added to a flame dried, 250 mL round bottom flask that was filled with argon. The reaction vessel was then cooled to –30 °C (reaction bath maintained between –33 °C and –30 °C) and then LDA (freshly prepared, 1 M in THF, 1.2 equiv) was added dropwise to the stirred enol ether over a 5 min period. The reaction mixture was allowed to stir at reduced temperature for 10 min and then placed directly into a cold bath maintained at –120 °C. The reaction vessel was stirred at –120 °C for 5 min and then the aldehyde (1.1 equiv) was added in one portion. The reaction mixture was stirred for an additional 10 min at this reduced temperature and then quenched by pouring into 100 mL of saturated aqueous $NaHCO_3$. An aqueous workup followed by flash column chromatography (silica gel) afforded the desired aldolate as a 5.5:1 mixture of diastereomers. Spectral data for aldol products: (**9b**, major): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (m, 1H), 5.18 (s, 1H), 4.98 (m, 2H), 3.90 (s, 3H), 3.37 (m, 1H), 3.35 (s, 1H), 3.12 (q, J = 7.74 Hz, 1H), 2.53 (m, 1H), 1.87 (dt, J = 13.8, 8.47 Hz, 1H), 1.55 (s, 1H), 1.48 (s, 9H), 1.28 (s, 3H), 1.27 (s, 3H), 1.05 (s, J = 6.91 Hz, 3H), 0.79 (d, J = 6.76 Hz, 3H); (minor): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (m, 1H), 5.19 (s, 1H), 5.06 (m, 2H). 1.48 (s, 3H), 3.41 (m, 1H), 3.17 (m, 1H), 3.12 (m, 1H), 2.11 (m, 1H), 1.86 (m, 1H), 1.63 (m, 1H), 1.48 (s, 9H), 1.28 (s, 3H), 1.27 (s, 3H), 1.07 (d, J = 6.91 Hz, 3H), 0.99 (d, J = 6.04 Hz, 3H).