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Total Synthesis of (+)-Herboxidiene from Two Chiral Lactate-Derived Ketones

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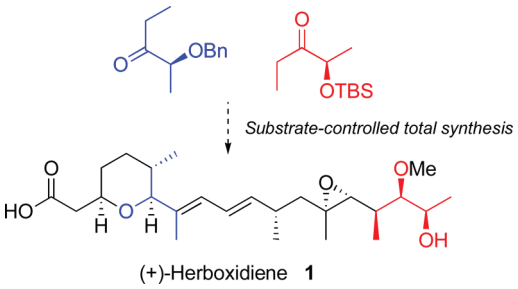
ABSTRACT



(+)-Herboxidiene **1**

A substrate-controlled synthesis of (+)-herboxidiene from two lactate-derived chiral ketones is described. Remarkably, most of the carbon backbone was constructed through highly stereoselective titanium-mediated aldol reactions and an Ireland–Claisen rearrangement. Furthermore, an *oxa*-Michael cyclization and a high-yield Suzuki coupling were used to assemble the pyran ring and the diene moiety respectively.

During the past few years, those engaged in the synthesis of natural products are paying increasing attention to the development of more efficient strategies and synthetic methodologies in the endless pursuit of the ideal synthesis.[1] Now, it is widely accepted that any synthetic endeavor should provide the target in a few steps and in high yields, taking advantage of selective transformations to assemble the carbon–carbon backbone and carbon–heteroatom bonds as well as minimizing manipulation of protecting groups and other functional groups.[1,2] With these ideas in mind, we envisaged that some titanium-mediated aldol methodologies developed by our group might pave the way to a new synthetic approach for (+)-herboxidiene (**1** in Scheme 1).

Isolated from *Streptomyces* sp. A7847 at Monsanto,[3] (+)-herboxidiene, also named GEX1A, was identified as a polyketide metabolite with potent and highly selective phytotoxic properties. It was later shown to affect plasma cholesterol[4] and to be active against several tumoral cell lines.[5] This appealing biological activity and its enticing structural features have attracted much attention, and several total syntheses have been reported.[6] Herein, we describe a very efficient synthesis based on highly stereoselective substrate-controlled reactions from two chiral lactate-derived ketones, without requiring any other source of chirality.

As outlined in Scheme 1, our retrosynthetic analysis for (+)-herboxidiene relies on the conversion of the epoxide to the corresponding alkene and the strategic disconnection of the C9–C10 bond. These early *transforms* provide two fragments of similar size and structural complexity, iodoalkene **2** and alkyne **3**, which could then be assembled through a palladium-catalyzed

(1) (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44–122. (b) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673.

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(6) (a) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955–968. (b) Banwell, M.; McLeod, M.; Premraj, R.; Simpson, G. *Pure Appl. Chem.* **2000**, *72*, 1631–1634. (c) Zhang, Y.; Panek, J. S. *Org. Lett.* **2007**, *9*, 3141–3143. (d) Murray, T. J.; Forsyth, C. J. *Org. Lett.* **2008**, *10*, 3429–3431. (e) Ghosh, A. K.; Li, J. *Org. Lett.* **2011**, *13*, 66–69.

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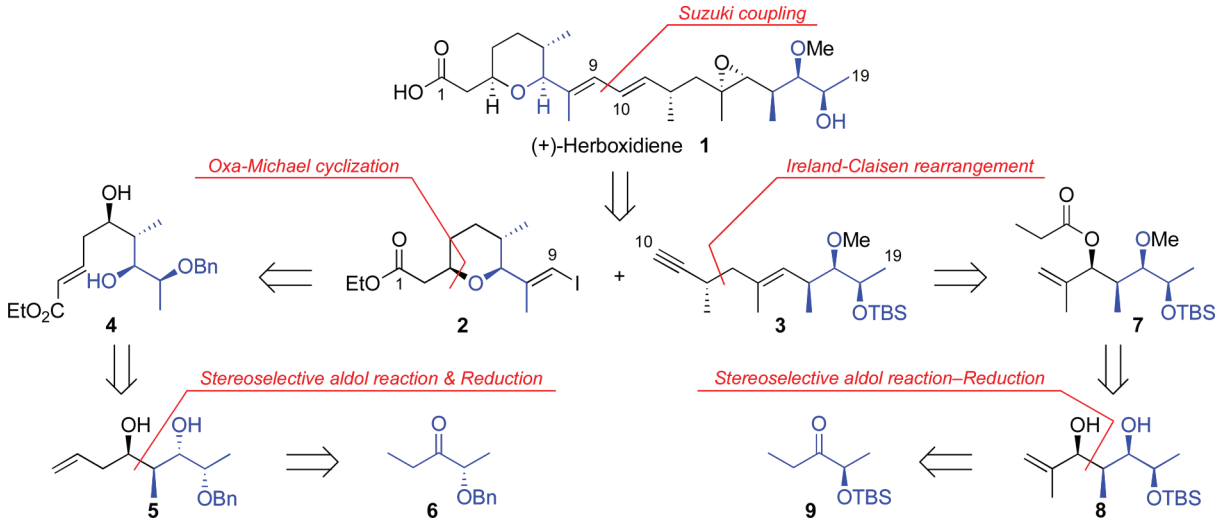
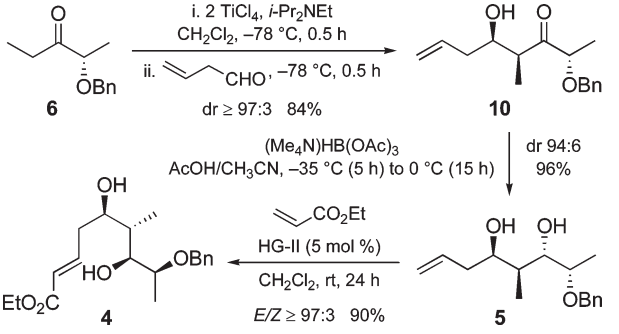
Scheme 1. Retrosynthetic Analysis of (+)-Herboxidiene



cross-coupling reaction. Following this analysis, we anticipated that the successful construction of **2** would mainly depend on an *oxa*-Michael cyclization of conjugated ester **4**, and a substrate-controlled aldol reaction from chiral ketone **6**, followed by reduction of the resulting aldol product to furnish diol **5**. Alkyne **3** would come from an Ireland–Claisen rearrangement of ester **7**, which could be prepared by selective functionalization of diol **8**. This, in turn, would arise through a stereoselective one-pot aldol–reduction transformation from chiral ketone **9**. In summary, our synthetic approach was based on a convergent strategy that depends on the stereocontrol provided by appropriate substrate-controlled reactions from intermediates represented in Scheme 1.

The synthesis of the C1–C9 fragment (**2**) began with the titanium-mediated aldol addition[7] of the lactate-derived ethyl ketone **6**[8] to 3-butenal[9] (Scheme 2). As expected, it afforded the aldol product **10** (dr ≥97:3 by ^{1}H NMR) in 84% yield, which was converted stereoselectively (dr 94:6, 96%) to diol **6** through an internal-hydride delivery using $(Me_4N)HB(OAc)_3$.[10] Finally, Hoveyda–Grubbs II catalyzed[11] cross-metathesis of diol **5** with ethyl acrylate furnished conjugated ester **4** in 90% yield ($E/Z \geq 97:3$). Hence, the stage was set for the construction of the pyran ring.

Scheme 2. Early Steps of the Synthesis of C1–C9 Fragment



Initially, we expected the *oxa*-Michael cyclization[12] of **4** to lead to *cis* pyran **11*c*** stereoselectively under thermodynamic conditions, since all the substituents in the six-membered heterocycle lie at equatorial positions (Scheme 3). Nevertheless, preliminary experiments with *t*-BuOK afforded *trans* pyran **11*t*** as the major diastereomer. After considerable investigation, we found that Fuwa's conditions (DBU, toluene, 100 °C)[13] provided an inseparable 1.8:1 mixture of **11*c***–**11*t*** diastereomers in 80% yield. Then, Barton–McCombie removal of the C5-hydroxy group under tin-free conditions,[14] followed by chromatographic purification of the reaction mixture, furnished the desired ester containing the *cis* pyran ring (**12*c***) in 54% yield. Importantly, treatment of the minor diastereomer **12*t*** with *t*-BuOK rendered **12c** as a single diastereomer in 61% yield,[15] which indicated that the hydroxyl group at C5 was responsible for the poor stereocontrol of the

(7) (a) Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519–522. (b) Solsona, J. G.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2004**, *45*, 5379–5382.

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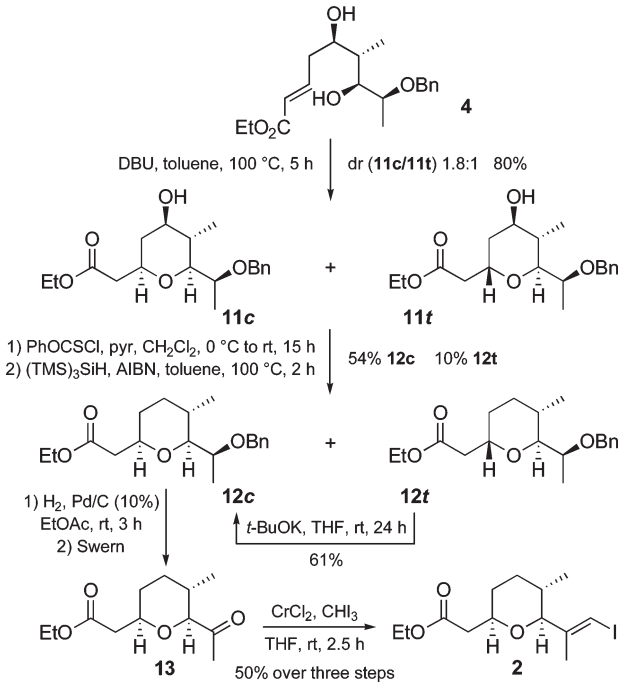
(14) Chatgilialoglu, C. *Chem.—Eur. J.* **2008**, *14*, 2310–2320.

(15) This retro-Michael reaction was not observed with DBU.

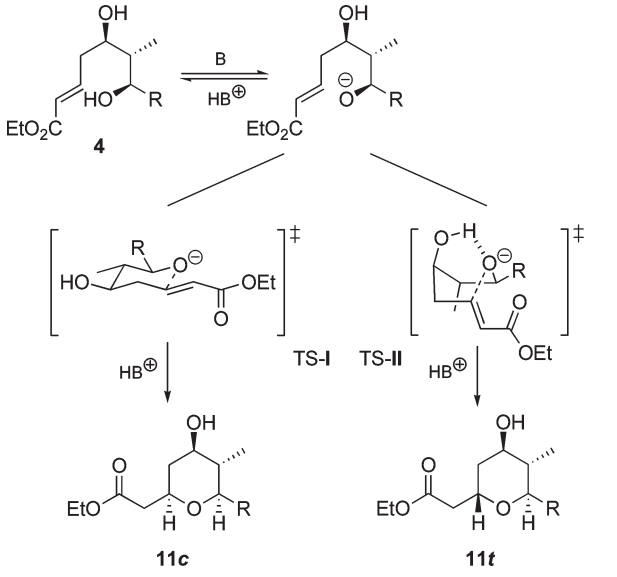
oxa-Michael cyclization. Finally, hydrogenolysis of the benzyl ether and Swern oxidation of the resultant alcohol afforded ketone **13**, which was submitted to Takai conditions[16] to deliver the C1−C9 fragment **2** in three steps, as an *E*/*Z* 90:10 mixture in 50% yield.

Scheme 3. Tetrahydropyran Construction and Final Steps of the Synthesis of C1−C9 Fragment



The lack of stereocontrol of the cyclization of a dihydroxy α,β-unsaturated ester such as **4** has been reported for a few related substrates.[17] Some of these precedents have also established that the protection of the C5 hydroxyl group allows the *cis* pyran to be obtained stereoselectively. Taking advantage of these reports and our own experience, and assuming that the cyclization to *cis* pyran **11*c*** must proceed through transition state TS-**I** in which all the substituents are placed at equatorial positions, we hypothesize that the poor stereoselective cyclization of **4** may be due to an intramolecular hydrogen bond that stabilizes the boat-like transition state TS-**II** leading to *trans* pyran **11*t*** (Scheme 4).[18]

Scheme 4. *Oxa*-Michael Cyclization of Dihydroxy Ester **4**



Having prepared the C1−C9 fragment, we focused on the synthesis of alkyne **3**, the C10−C19 fragment (see Scheme 1). We envisaged that it could be constructed from a sequential transformation consisting of a highly stereoselective titanium-mediated aldol addition of chiral ketone **9**[8] to methacrolein followed by reduction of the resultant aldolate with $LiBH_4$.[19] As expected, this one-pot transformation afforded all *syn* diol **8** (dr ≥97:3 by ^1H NMR) in 81% yield (Scheme 5). Remarkably, the four stereocenters required for the synthesis of **3** had been installed in a single step with absolute stereocontrol. Then, selective monoacylation of the less sterically hindered hydroxyl group of **8** using Clarke's conditions[20] and methylation of the resulting hydroxy ester with $(Me_3O)BF_4$/proton sponge furnished key intermediate **7** in 66% yield. The crucial Ireland−Claisen rearrangement was next addressed.[21] After a thorough optimization, it was found that treatment of **7** with LiHMDS in 4:1 THF/DMPU at −78 °C produced a lithium enolate that could be trapped with TBSCl.[22] Then, the resulting ketene silyl acetal underwent a clean [3,3] sigmatropic rearrangement to furnish a silyl ester, which was reduced with $LiAlH_4$ to afford alcohol **14** as a single diastereomer (dr ≥97:3 by ^1H NMR). Swern

(16) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.

(17) For related unexpected lack of stereocontrol of oxa-Michael cyclizations, see: (a) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826. (b) Bates, R. W.; Song, P. *Synthesis* **2010**, 2935–2942. (c) Wang, B.; Hansen, T. M.; Wang, T.; Wu, D.; Weyer, L.; Ying, L.; Engler, M. M.; Sanville, M.; Leitheiser, C.; Christmann, M.; Lu, Y.; Chen, J.; Zunker, N.; Cink, R. D.; Ahmed, F.; Lee, C.-S.; Forsyth, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1484–1505. (d) Ferrié, L.; Boulard, L.; Pradaux, F.; Bouzbouz, S.; Reymond, S.; Capdevielle, P.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 1864–1880.

(18) Although intramolecular hydrogen bonds have never been invoked to rationalize the stereochemical outcome of an oxa-Michael cyclization, there are reports about the role of metal chelation on such transformations: (a) Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2618–2620. (b) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2011**, *13*, 1820–1823.

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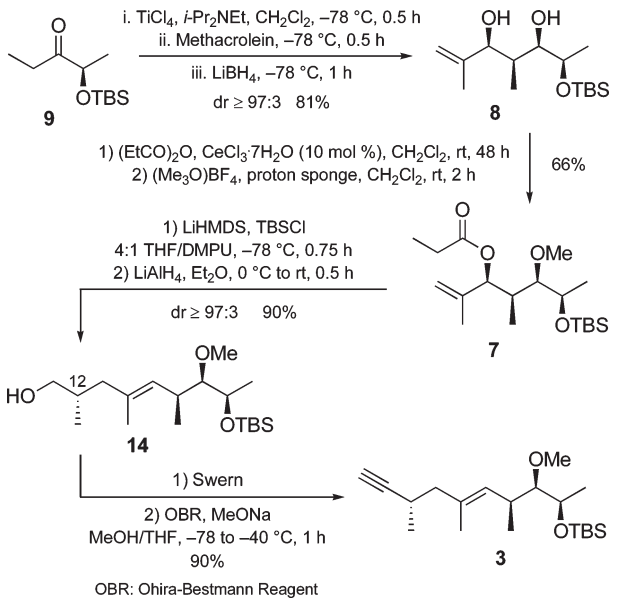
(20) (a) Clarke, P. A. *Tetrahedron Lett.* **2002**, *43*, 4761–4763. (b) Clarke, P. A.; Kayaleh, N. E.; Smith, M. A.; Baker, J. R.; Bird, S. J.; Chan, C. *J. Org. Chem.* **2002**, *67*, 5226–5231.

(21) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650–657.

(22) Magauer, T.; Martin, H. J.; Mulzer, J. *Chem.—Eur. J.* **2010**, *16*, 507–519.

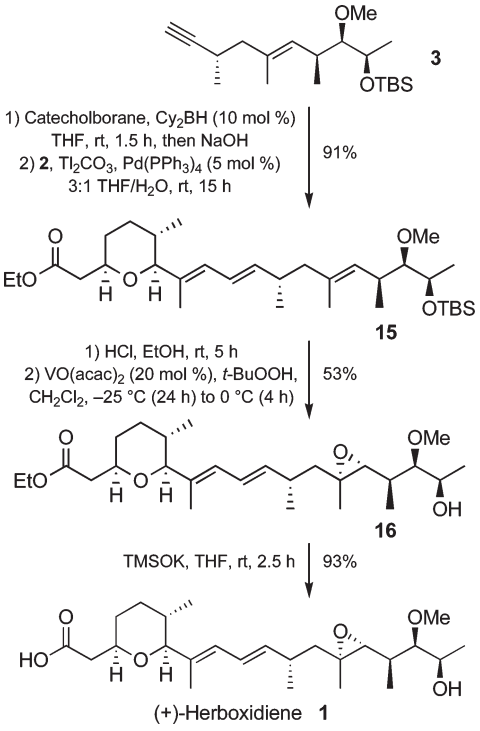
oxidation of **14** and treatment of the resultant aldehyde under modified Ohira–Bestmann conditions[23] delivered **3** as a single diastereomer in 90% yield. Importantly, the latter reaction was carried out at −78 °C to avoid epimerization of the C12-stereocenter.[24]

Scheme 5. Synthesis of C10–C19 Fragment



With both fragments **2** and **3** in hand, we faced the construction of the diene moiety (Scheme 6). After exploring several possibilities, we found that the most efficient approach involved hydroboration of **3** with catecholborane in the presence of catalytic amounts of dicyclohexylborane, followed by hydrolysis of the resultant boronate to give the corresponding boronic acid (Arase conditions).[25] Suzuki coupling of this boronic acid and iodoalkene **2** proceeded in a straightforward manner and provided diene **15** in 91% yield.[26] Having prepared the carbon backbone of (+)-herboxidiene, the endgame entailed removal of the silyl ether and epoxidation of the resultant bis-homoallylic alcohol as described in previous syntheses[6] (53% yield). Finally, saponification of ethyl ester **16** with TMSOK[27] furnished (+)-herboxidiene in 93% yield.[28]

Scheme 6. Assembly of Fragments **2** and **3** and Endgame



In summary, the synthesis of (+)-herboxidiene **1** has been accomplished from two lactate-derived chiral ketones, without requiring other sources of chirality, in a 14-step sequence and 8% overall yield. Most of these steps involve highly stereoselective carbon–carbon (aldol reactions, Ireland–Claisen rearrangement, Suzuki coupling) or carbon–oxygen (*oxa*-Michael cyclization) bond-forming reactions, and other strategic redox processes. These features, the lack of protecting groups (the only protecting groups used along the whole synthesis are placed in the starting chiral ketones), and the reduced number of *concession steps* give this substrate-controlled synthesis a high ideality number (57%) according to Baran's definition.[1b]

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Supporting Information Available. Experimental procedures and physical and spectroscopic data, including copies of ^{1}H and ^{13}C NMR spectra and proofs of the stereochemistry of **11c** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Spectroscopic data of synthetic **1** matched those previously reported. See Supporting Information.