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Diastereoselective Intramolecular Diels-Alder Reactions towards the Synthesis of a Taxol C-Ring Precursor

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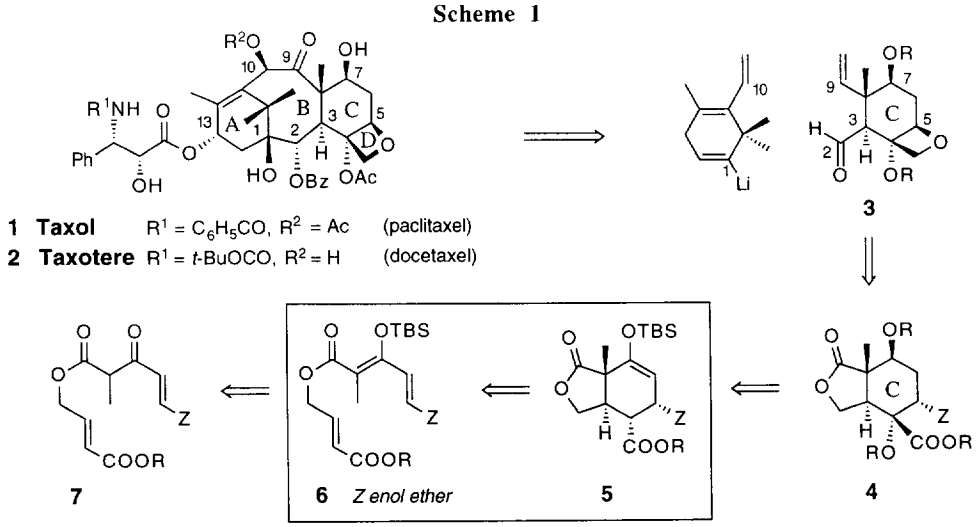
Abstract: Intramolecular Diels-Alder reactions have been used for the synthesis of *cis*-hydroisobenzofuranones **23** or **21**, which represents a potential precursor of taxol C-ring. Easy preparation of β-ketoesters **7a** and **7b** is also described. © 1997 Elsevier Science Ltd.

Taxol **1**®[1] and taxotere **2**®[2] have triggered considerable interest among biologists and chemists, owing to their remarkable anti-cancerous activity and their challenging structure. Although numerous studies have been devoted to the construction of the taxoid ring-system,[3] only four total syntheses of taxol have been reported.[4]

In the course of our studies towards the synthesis of taxoid derivatives, we are currently exploring several convergent approaches.[5] One of these routes involving a ring closure by an olefin metathesis reaction between C9 and C10 is described below (Scheme 1). The potential efficiency of this approach relies on two points: - synthesis of a highly functionalized C-ring bearing all required stereocenters; - coupling with an achiral A-ring, followed by introduction of the remaining stereocenters by diastereoselective reactions.

Scheme 1



1 Taxol $R^1 = C_6H_5CO$, R^2 = Ac (paclitaxel)
2 Taxotere R^1 = *t*-BuOCO, R^2 = H (docetaxel)

3 **4** **5** **6** *Z enol ether* **7**

C-ring **3** would be prepared from lactone **4**, where Z is a potential leaving group for the formation of the oxetane ring: a thioaryl group is a good candidate for this group, as it is easily converted to a sulfonium moiety with methyl iodide. Lactone **5** can be synthesized from β-ketoester **7** *via* silyl enol ether **6** by an intramolecular

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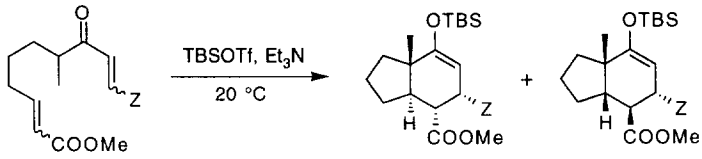
Diels-Alder reaction. If the transition state of this cyclization is assumed to be *endo*, the Z geometry is required for the silyl enol ether in order to obtain the desired *trans* ring junction. An intramolecular Mukaiyama-Michael reaction could also be envisaged to perform the double ring-closure. Fukumoto[6] has shown that the stereoselectivity of such a cyclization in the formation of hydrindenes from ketone **8** does not depend on the geometry of the olefins involved in the reaction (Scheme 2).

Scheme 2



8

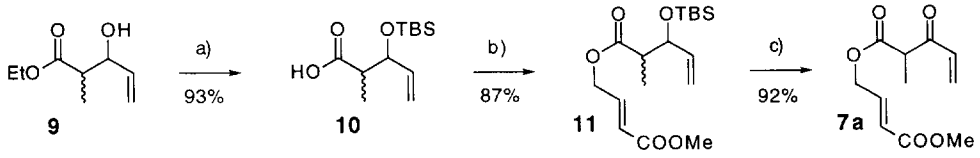
	yield	*trans/cis*
Z = H	0%	
Z = SPh	47-62%	*5 : 1*
Z = S-*p*MeOPh	79-81%	*7 : 1*

To our knowledge, no example of this kind of reactions applied to β-ketoesters such as **7** has been reported, and we wished to study the feasibility and the stereochemical course of these cyclizations. We describe here the synthesis of a bicyclic compound which could be transformed into a suitable precursor of taxol C-ring.

PREPARATION OF β-KETOESTERS 7a AND 7b

The first goal was to construct the precursors to these two cyclisations, β-ketoesters **7a** and **7b**. Two Z groups were chosen for this purpose, Z = *p*-$MeOC_6H_4S$ and the simpler one Z = H. In the latter case, synthesis is straightforward (Scheme 3). Alcohol **9**[7] (*syn/anti* = 1:1) was protected as a silyl ether and the ester function hydrolyzed in 93% yield for the two steps. The resulting acid **10** was then coupled with (*E*)-methyl 4-hydroxycrotonate[8] in good yield. Deprotection of silyl ether **11** with aqueous HF in acetonitrile, followed by oxidation of the resulting alcohol with Jones' reagent, furnished β-ketoester **7a** in 92% yield. Addition of 2,2,6,6-tetramethylpiperidine oxide was necessary in order to avoid polymerization of ketoester **7a**. This compound was used without purification as it was too unstable for column chromatography.

Scheme 3



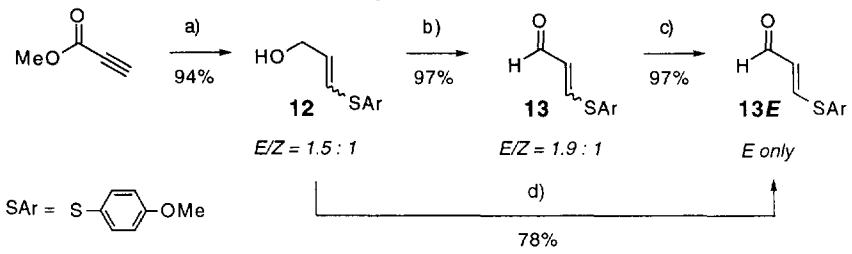
9 **10** **11** **7a**

a) i- TBSOTf, Et_3N; ii- KOH, MeOH; HCl. **b)** (*E*)-Methyl 4-hydroxycrotonate, DCC, DMAP. **c)** i- HF, CH_3CN; ii- Jones' reagent, TEMPO.

For **7b** where Z = *p*-$MeOC_6H_4S$, aldehyde **13*E*** was first synthesized (Scheme 4). Methyl propiolate was treated with *p*-methoxybenzene thiol in the presence of a catalytic amount of triethylamine to afford a 1.5:1 mixture of *E*:Z unsaturated esters,[9] which were reduced by DIBAL-H to give alcohols **12** in excellent yield. When these alcohols were oxidized by the Dess-Martin periodinane,[10] aldehyde **13*E*** was obtained as a single

isomer in 78% yield. If *o*-iodoxybenzoic acid (IBX)[11] was used, aldehydes **13** were produced in 97% yield in a 1.9:1 ratio.[9] Reasoning that the olefin was probably equilibrating in the presence of pyridine and acetic acid (released by the Dess-Martin reagent), we submitted aldehydes **13** to these conditions. Gratifyingly, aldehyde **13*E*** was obtained almost exclusively (**13*E*/13*Z*** = 35:1)[12] and could be isolated in pure form after recrystallisation (94% for the two operations).

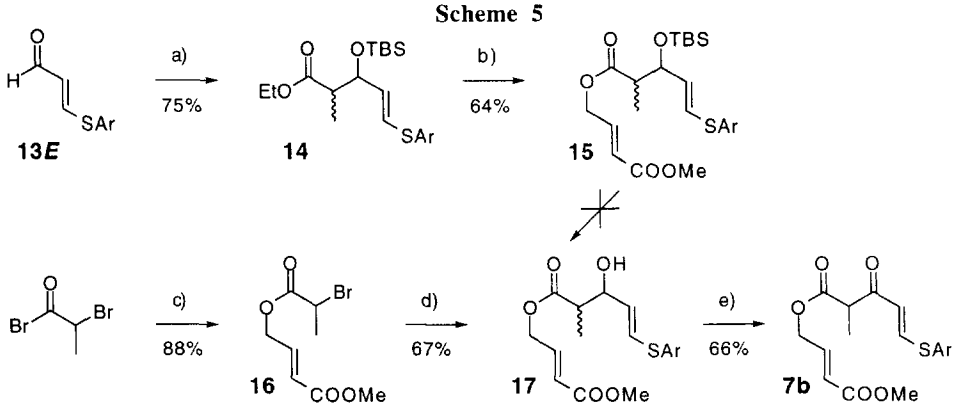
Scheme 4



a) i- ArSH, Et_3N; ii- DIBAL-H. **b)** IBX, DMSO, THF. **c)** Py, AcOH; recrystallisation. **d)** Dess-Martin periodinane, Py.

Synthesis of **15** from **13*E*** was first attempted according to the preceding route. Condensation of the lithium enolate of ethyl propionate with aldehyde **13*E*** followed by protection of the resulting alcohol as a silyl ether afforded ester **14** as a 1:1 mixture of *syn*/*anti* diastereomers (Scheme 5). Compound **14** was then converted to the corresponding acid, which was coupled with methyl 4-hydroxycrotonate as before to give silyl ether **15** in 64% yield for the two steps. At this point, all attempts to remove the TBS group failed. The use of other protecting groups met with little success, and when the hydroxyl group was left unprotected, the coupling step did not proceed in good yield.

Scheme 5



a) i- Ethyl propionate, LDA; ii- TBSOTf, Et_3N. **b)** i- KOH, MeOH; HCl; ii- *E*-Methyl 4-hydroxycrotonate, DCC, DMAP. **c)** (*E*)-Methyl 4-hydroxycrotonate, Py. **d)** **13*E***, Zn, THF, ultrasound, 55 °C. **e)** Dess-Martin periodinane, Py.

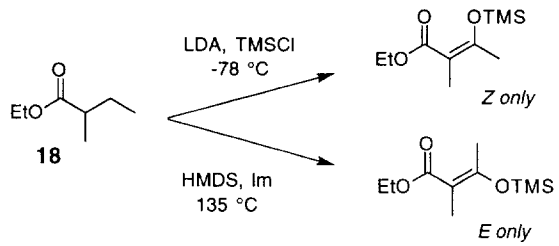
We then turned to a route where no alcohol protection would be needed, because the hydroxyl group would be installed immediately prior to the oxidation leading to the desired β-ketoester. Reaction of 2-bromopropionyl bromide with methyl 4-hydroxycrotonate in pyridine afforded bromide **16** in 88% yield. Reformatsky coupling[13] of **16** with aldehyde **13*E*** gave alcohol **17** which could be oxidized into the desired

β-ketoester **7b** with the Dess-Martin periodinane.

CYCLIZATION REACTIONS FOR Z = SAr

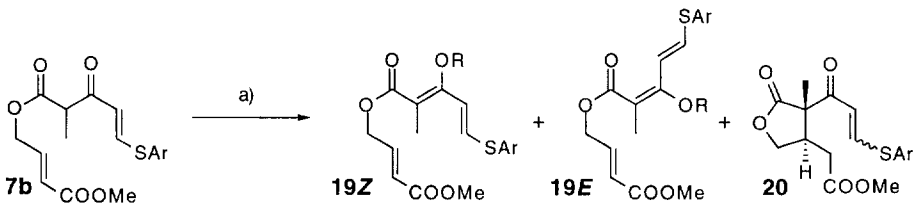
With both β-ketoesters **7a** and **7b** in hand, we examined the preparation of the derived silyl enol ethers in view of intramolecular Diels-Alder cyclizations. Few examples of formation of silyl enol ethers derived from 2-substituted β-ketoesters have been described. Gilbert[14] reports that ketoester **18**, when treated with LDA and TMSCl, produces exclusively the *Z* silyl enol ether, whereas use of HMDS and imidazole at 135 °C leads to the thermodynamically favored *E* silyl enol ether (Scheme 6).

Scheme 6



Disappointingly, treatment of ketoester **7b** with LDA and TMSCl furnished none of the desired silyl enol ether but led to the cyclic product **20** (Scheme 7). Michael addition of the ketoester enolate onto the unsaturated

Scheme 7



a)	R	Conditions	Results
	TMS	1) LDA or NaH 2) TMSCl	**20** only
		1) TMSCl 2) LDA or NaH	**19*Z***
	TES	1) TESCl 2) NaH	mixture of **19*Z*** and **20**
	TBS	1) TBSCl 2) NaH	**20** only
	TBS	1) Et_3N 2) TBSOTf	46% (**19*E***), ***Z*** / ***E*** = 1 : 6

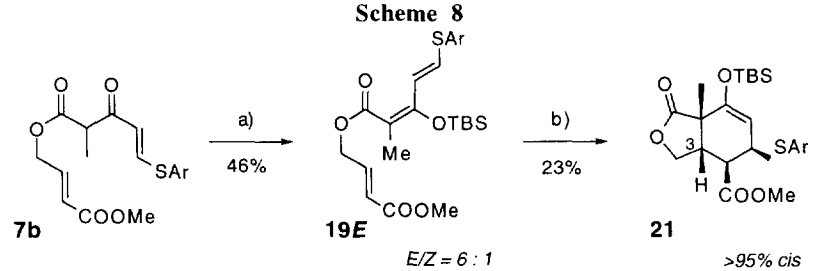
ester of the crotyl residue seems to be faster than formation of the silyl enol ether. *E/Z* isomerization of the thioaryl double bond in **20** could be due to a reversible second cyclization. All attempts to convert compound **20** into a bicyclic product with bases such as LDA or NaH[15] failed.

When TMSCl was added before the base, **19Z** could be observed by NMR with no trace of **20**, but unfortunately this silyl enol ether was too unstable to be isolated. Use of a more hindered silyl group like TES led to a mixture of **19Z** and **20**, and with TBSCl only **20** was produced.

The rate of formation of the silyl enol ether was thus shown to depend on the silyl group: if this group is small and reactive (TMS), the silyl enol ether is formed faster than cyclic product **20**, but in this case the desired product cannot be isolated. If the silyl group is larger and less reactive (TES or TBS), the silyl enol ether produced is more stable but the intramolecular reaction becomes competitive. Finally, under Fukumoto's conditions (TBSOTf/Et_3N), silyl enol ether **19** was obtained as a 6:1 mixture of *E* and *Z* isomers,[16] from which the major isomer was isolated in 46% yield; no monocyclic or bicyclic product was formed starting from ketoester **7b**. In our case, the β-ketoester silyl enol ether (*versus* Fukumoto's ketone silyl enol ether) is probably not reactive enough to undergo a cyclization reaction.

Despite the impossibility to obtain pure silyl enol ether **19Z**, we nevertheless decided to attempt a Diels-Alder cyclization on **19*E***, as it is possible to invert the stereochemistry at C3 at a later stage of the synthesis (after lactone opening, the resulting primary alcohol would be converted to the corresponding aldehyde and the adjacent center could be epimerized). Heating **19*E*** in toluene for four days afforded bicylic compound **21** in 23% yield as a single diastereomer (Scheme 8). The stereochemistry of **21** was proved by NOESY NMR; in

Scheme 8



7b **19*E*** *E/Z = 6 : 1* **21** *>95% cis*

a) TBSOTf, Et_3N. **b)** Toluene, Δ.

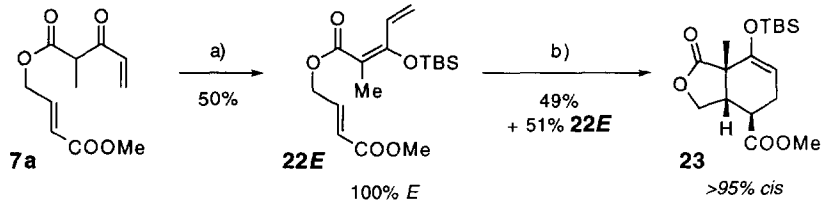
particular, a nOe effect between the angular methyl group and the ring-junction proton indicated their *cis* relationship. The poor yield is due to competitive decomposition of the silyl enol ether as loss of the thioaryl group was observed.

CYCLIZATION REACTIONS FOR Z = H

Since γ-thioaryl silyl enol ether **19*E*** seemed to be too unstable, we next turned to the simpler ketoester **7a**, where Z = H (Scheme 9). Danishefsky showed that it is possible to obtain the oxetane D-ring of taxol from the unsaturated ester at C4.[17] Thus compound **23** could be fitted with the functional groups present in taxol C-ring at a later stage of the synthesis. In this case again, the required *Z* enolate could not be obtained: under strongly basic conditions, only polymerization occured. Use of TBSOTf/Et_3N led mostly to decomposition products, along with a small amount (15%) of compound **22*E***. We were however delighted to see that treatment of **7a** with TBSCl and triethylamine in ether[18] gave enol ether **22*E*** in 50% yield.[14] This diene, when heated in toluene for four days, afforded bicyclic compound **23** in 49% yield, along with 51% of recovered **22*E***. As

before, stereoselectivity of the reaction was excellent, and only the *cis* ring junction was observed.

Scheme 9



a) TBSCl, Et_3N, Et_2O, DMAP. **b)** Toluene, Δ.

In summary, bicyclic compounds **21** and **23** have been obtained form the *E* silyl enol ethers **19*E*** and **22*E*** in 23% and 49% yield respectively. Non-bonding interactions resulting from the incipient angular methyl group are probably responsible for the modest yields of these cyclizations.[19] In each case only one diastereomer was observed, with a *cis* ring-junction, confirming that the reaction proceeds as expected *via* an *endo* transition state. To our knowledge, this is the first example of intramolecular Diels-Alder reactions involving a β-ketoester silyl enol ether as the diene component. Current efforts are devoted to apply this methodology for the enantioselective construction of taxol C-ring.

EXPERIMENTAL SECTION

General methods

Physical data and spectroscopic measurements

Melting points (mp) were determined on a REICHERT apparatus and are uncorrected. ^1H NMR spectra were recorded on a BRUKER WP 200 (200 MHz), or on a BRUKER AM 400 (400 MHz) instrument. ^{13}C NMR spectra were recorded on the same instruments at 50 MHz and 100 MHz respectively. Mass spectra (MS) were obtained on a HEWLETT-PACKARD HP 5989B spectrometer *via* either direct introduction or GC/MS coupling with a HEWLETT-PACKARD HP 5890 chromatograph. Ionisation was obtained either by electronic impact (EI) or chemical ionisation with ammonia (IC, NH_3). Infrared spectra (IR) were obtained on a PERKIN-ELMER FT 1600 instrument using either NaCl salt plates (thin film) or NaCl cell (in the specified solvent). Microanalyses were performed by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, C.N.R.S., F-91198, Gif sur Yvette.

Chromatography

All reactions were monitored by thin-layer chromatography (TLC) carried out on E.MERCK Ref. 5549 or 5554 silica gel precoated silica gel 60F 254 plates. Visualisation was accomplished with UV light then 7-10% ethanolic phosphomolybdic acid solution, anisaldehyde solution, or ceric ammonium molybdate solution followed by heating were used as developing agents. Flash chromatography was performed on E. MERCK silica gel Si 60 (40-63 μm, Ref. 9385). The solvents used for elution were not distilled except petroleum ether and ethyl acetate.

Solvents distillation

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone. Dichloromethane (CH_2Cl_2) and amines were distilled from calcium hydride. Benzene (PhH) and toluene were

distilled from sodium-benzophenone. Dimethylformamide (DMF) was distilled from magnesium sulfate under reduced pressure.

Ethyl (2*R,3*R**)-3-*tert*-Butyldimethylsiloxy-2-methylpent-4-enoate**

To a solution of 17.33 g (109.6 mmol) of alcohol **9** in 300 mL of CH_2Cl_2 at - 78 °C was added 16.8 mL (121 mmol, 1.10 equiv) of triethylamine, followed by 26.4 mL (115 mmol, 1.05 equiv) of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). The reaction mixture was stirred at -78 °C for 30 min, and treated with 4.6 mL (33 mmol, 0.3 equiv) of triethylamine and 5.0 mL (22 mmol, 0.2 equiv) of TBSOTf and the resulting solution was stirred at this temperature for 15 min before addition of 10 mL of methanol, and 200 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with 2 x 200 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (40:60 diethyl ether/petroleum ether) afforded 29.85 g (quantitative) of the desired silyl ether as a colorless oil (1:1 mixture of diastereomers): IR (thin film) 2956, 2930, 2886, 2857, 1738, 1645, 1472, 1463, 1422, 1404, 1389, 1372, 1362, 1336, 1302, 1255, 1185, 1149, 1118, 1078, 1032, 1006 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.0, 10.2, 6.4 Hz, 0.5H, H-4), 5.71 (ddd, *J* = 17.4, 10.2, 7.3 Hz, 0.5H, H-4), 5.23-5.06 (m, 2H, H_2-5), 4.40-4.34 (m, 0.5H, H-3), 4.28-4.21 (m, 0.5H, H-3), 4.18-4.04 (m, 2H, OCH_2CH_3), 2.55-2.45 (m, 1H, H-2), 1.23 (td, *J* = 7.1, 2.8 Hz, 3H, OCH_2CH_3), 1.14 (d, *J* = 7.0 Hz, 1.5H, CH_3-2), 1.03 (d, *J* = 7.1 Hz, 1.5H, CH_3-2), 0.87, 0.85 (2s, 9H, $SiC(CH_3)_3$), 0.03, 0.01 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.7, 174.2 (C-1), 139.5, 138.7 (C-4), 116.5, 115.3 (C-5), 76.2, 75.1 (C-3), 60.1 (OCH_2CH_3), 46.8, 46.7 (C-2), 25.7 ($SiC(CH_3)_3$), 18.1, 18.0 ($SiC(CH_3)_3$), 14.1 (OCH_2CH_3), 12.7, 11.7 (CH_3-2), -3.0 -4.3, -5.2 ($Si(CH_3)_2$). Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.71; H, 10.36. Found: C, 61.84; H, 10.26.

(2*RS*, 3*R**)-3-*tert*-Butyldimethylsiloxy-2-methylpent-4-enoic acid 10**

A solution of 29.85 g (109.6 mmol) of the above ester in 275 mL of methanol and 55 mL of 40% aqueous KOH was heated at 70 °C for 5 h. It was then cooled to 20 °C and the methanol was evaporated *in vacuo*. The residue was partitioned between 200 mL of diethyl ether and 200 mL of water, and the layers were separated. The aqueous phase was washed with 50 mL of diethyl ether, acidified to pH 2 with *ca.* 120 mL of 4 N aqueous HCl, and extracted with 3 x 200 mL of diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 24.39 g (93%) of acid **10** as a colorless oil (1:1 mixture of diastereomers): IR (thin film) 2930, 2858, 1713, 1644, 1472, 1462, 1422, 1389, 1362, 1334, 1255, 1223, 1085, 1029, 1006 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 13.6, 10.3, 6.4 Hz, 0.5H, H-4), 5.73 (ddd, *J* = 14.2, 10.2, 7.2 Hz, 0.5H, H-4), 5.28-5.13 (m, 2H, H-5), 4.45-4.39 (m, 0.5H, H-3), 4.29-4.22 (m, 0.5H, H-3), 2.61-2.53 (m, 1H, H-2), 1.15 (d, *J* = 6.9 Hz, 1.5H, CH_3-2), 1.10 (d, *J* = 7.2 Hz, 1.5H, CH_3-2), 0.89, 0.87 (2s, 9H, $SiC(CH_3)_3$), 0.07, 0.06, 0.04, 0.03 (4s, 6H, $Si(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.0, 178.7 (C-1), 138.3, 138.0 (C-4), 117.0, 116.5 (C-5), 76.1, 75.1 (C-3), 46.8, 46.1 (C-2), 25.7 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 12.9, 11.3 (CH_3-2), -4.1, -5.0 ($Si(CH_3)_2$); MS (CI, NH_3) *m/z* 262 ($MH^+ + NH_3$), 245 (MH^+).

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*RS*,3*R**)-3-*tert*-Butyldimethylsiloxy-2-methylpent-4-enoate 11**

To a solution of 595 mg (2.44 mmol) of acid **10** and 283 mg (2.44 mmol) of (*E*)-methyl 4-hydroxycrotonate[8] in 25 mL of CH_2Cl_2 was added 553 mg (2.68 mmol, 1.10 equiv) of dicyclohexylcarbodiimide (DCC), followed by a few crystals of 4-dimethylaminopyridine (DMAP). The cloudy

mixture was stirred at 20 °C for 16 h, and then filtered through cotton, rinsing with petroleum ether. The filtrate was partitioned between 50 mL of diethyl ether and 50 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (25:75 diethyl ether/petroleum ether) gave 726 mg (87%) of ester **11** as a colorless oil (1:1 mixture of diastereomers): IR (thin film) 2954, 2886, 2857, 1731, 1668, 1472, 1462, 1436, 1404, 1385, 1361, 1310, 1255, 1171, 1081, 1028, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.6, 5.8 Hz, 0.5H, H-2'), 6.94 (dt, *J* = 15.9, 4.8 Hz, 0.5H, H-2'), 6.08-6.02 (m, 1H, H-3'), 5.81 (ddd, *J* = 17.1, 10.4, 6.7 Hz, 0.5H, H-4), 5.71 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 0.5H, H-4), 5.22-5.10 (m, 2H, H-5), 4.74-4.70 (m, 2H, H_2-1'), 4.40-4.37, 4.26-4.22 (2m, 1H, H-3), 3.75 (s, 3H, OCH_3), 2.61-2.58 (m, 1H, H-2), 1.17, 1.07 (2d, *J* = 7.1 Hz, 3H, CH_3-2), 0.87, 0.84 (2s, 9H, $SiC(CH_3)_3$), 0.02, 0.01 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.6 (C-1), 166.3 (C-4'), 141.5 (C-2'), 139.1, 138.5 (C-4), 121.8 (C-3'), 117.1, 115.9 (C-5), 76.4, 75.0 (C-3), 62.4 (C-1'), 51.7 (OCH_3), 46.8, 46.7 (C-2), 25.7 ($SiC(\mathbf{C}H_3)_3$), 18.1, 18.0 ($Si\mathbf{C}(CH_3)_3$), 13.1, 11.6 (CH_3-2), -4.2, -4.3, -5.3 ($Si(CH_3)_2$). Anal. Calcd for $C_{17}H_{30}O_5Si$: C, 59.61; H, 8.83. Found: C, 59.88; H, 8.71.

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*RS*,3*R**)-3-Hydroxy-2-methylpent-4-enoate**

To 726 mg (2.12 mmol) of ester **11** was added 20 mL of a 95:5 CH_3CN/40% aqueous HF solution. The resulting solution was stirred at 20 °C for 2.5 h, and then partitioned between 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (70:30, 80:20 diethyl ether/petroleum ether) gave 457 mg (94%) of the desired alcohol as a colorless oil (1:1 mixture of diastereomers): IR (thin film) 3499, 2983, 2950, 2883, 1726, 1667, 1437, 1385, 1314, 1279, 1174, 1111, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (dt, *J* = 15.7, 4.5 Hz, 1H, H-2'), 6.02, 5.99 (2dt, *J* = 15.7, 1.9 Hz, 1H, H-3'), 5.84-5.74 (m, 1H, H-4), 5.28-5.23 (m, 1H, H-5), 5.18-5.13 (m, 1H, H-5), 4.74-4.71 (m, 2H, H_2-1'), 4.40-4.37, 4.19-4.16 (2m, 1H, H-3), 3.69 (s, 3H, OCH3), 2.90 (br s, 1H, OH), 2.64 (ddd, *J* = 14.4, 7.1, 4.7 Hz, 0.5H, H-2), 2.58 (dt, *J* = 14.6, 7.3 Hz, 0.5H, H-2), 1.15 (d, *J* = 7.0 Hz, 1.5H, CH_3-2), 1.13 (d, *J* = 7.1 Hz, 1.5H, CH_3-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 174.2 (C-1), 166.2 (C-4'), 141.3, 141.2 (C-2'), 137.8, 137.4 (C-4), 121.7, 121.6 (C-3'), 117.2, 116.3 (C-5), 74.7, 73.0 (C-3), 62.5 (C-1'), 51.6 (OCH_3), 45.3, 44.7 (C-2), 13.7, 11.1 (CH_3-2). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.15; H, 6.91.

(2*E*)-3-Methoxycarbonylprop-2-enyl 2-Methyl-3-oxopent-4-enoate 7a

To a solution of 2.25 g (9.88 mmol) of the above alcohol in 50 mL of acetone at 0 °C was added 6.4 mL (13 mmol, 1.3 equiv) of 2 M Jones' reagent and a few crystals of 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO). The orange reaction mixture was stirred at 0 °C for 10 min, and treated with methanol dropwise until it turned green. It was then partitioned between 250 mL of iced water and 250 mL of diethyl ether, and the layers were separated. The aqueous phase was extracted with 2 x 250 mL of ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 2.19 g (98%) of β-ketoester **7a** which was used without purification for the next step (ketone/enol = 3:1): IR (thin film) 2988, 2950, 1726, 1667, 1652, 1613, 1575, 1437, 1399, 1383, 1312, 1279, 1237, 1195, 1174, 1086, 1039 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.06-6.82 (m, 1H, H-2' keto and enol), 6.70-5.89 (m, 0.75H, H-4, H-5*trans*, H-3' enol), 6.49-6.39 (m, 0.75H, H-4 keto), 6.10-5.96 (m, 1.5H, H-3', H-5*trans* keto), 5.92 (d, *J* = 9.8, 1.7 Hz, 0.75H, H-5*cis* keto), 5.60 (d, *J* = 10.8, 1.7 Hz, 0.25H, H-5*cis* enol), 4.86 (dd, *J* = 4.3, 2.1 Hz,

0.5H, H_2-1' enol), 4.79 (dd, J = 4.6, 1.8 Hz, 1.5H, H_2-1' keto), 3.88 (m, 0.75H, H-2 keto), 3.76 (s, 0.75H, OCH_3 enol), 3.75 (s, 2.25H, OCH_3 keto), 1.90 (s, 0.75H, CH_3-2 enol), 1.42 (d, J = 7.3 Hz, 2.25H, CH_3-2 keto).

Methyl 3-(4-Methoxyphenylthio)prop-2-enoate

To a solution of 1.4 g (10 mmol) of 4-methoxybenzene thiol in 10 mL of benzene at 20 °C was added a catalytic amount of triethylamine. After stirrring for 15 min at 20 °C, the mixture was cooled to 0 °C and treated with 990 µl (11 mmol, 1.1 equiv) of methyl propiolate. The reaction mixture was stirred at 0 °C for 1 h and partitioned between 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (20:80, 30:70, 40:60 diethyl ether/petroleum ether) gave 2.3 g (quantitative) of the desired ester as a yellow oil (1.5:1 mixture of *E*/*Z* isomers): IR (thin film) 3001, 2948, 2905, 2837, 1709, 1627, 1585, 1495, 1462, 1436, 1407, 1360, 1290, 1249, 1218, 1164, 1106, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, J = 14.9 Hz, 0.6H, H-3 *E*), 7.44-7.38 (m, 2H, Ar-H *E* and *Z*), 7.18 (d, J = 10.1 Hz, 0.4H, H-3 *Z*), 6.95-6.87 (m, 2H, Ar-H *E* and *Z*), 5.85 (d, J = 10.1 Hz, 0.4H, H-2 *Z*), 5.49 (d, J = 14.9 Hz, 0.6H, H-2 *E*), 3.83, 3.68 (2s, 2.4H, OCH_3 *Z*), 3.82, 3.78 (2s, 3.6H, OCH_3 *E*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8 (C-1 *E*), 165.6 (C-1 *Z*), 160.6 (C-4' *Z*), 159.9 (C-4' *E*), 151.8 (C-3 *E*), 148.4 (C-3 *Z*), 135.4 (C-2', C-6' *Z*), 133.3 (C-2', C-6' *E*), 126.5 (C-1' *E*), 119.9 (C-1' *Z*), 115.2 (C-3', C-5' *Z*), 114.5 (C-3', C-5' *E*), 114.0 (C-2 *Z*), 112.0 (C-2 *E*), 55.2 ($ArOCH_3$ *E* and *Z*), 51.2 (OCH_3 *E* and *Z*). Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39. Found: C, 59.09; H, 5.54.

3-(4-Methoxyphenylthio)prop-2-en-1-ol 12

To a solution of 11 g (50 mmol) of the above ester in 200 mL of diethyl ether at -78 °C was added slowly 150 mL (150 mmol, 3.0 equiv) of 1 M diisobutylaluminium hydride in hexane. The resulting solution was stirred at -78 °C for 2 h, treated with 10 mL of ethyl acetate, and warmed to 20 °C. At this point, 350 mL of 10% aqueous sodium potassium tartrate was added and the two-phase mixture was stirred at 20 °C for 1.5 h. The layers were separated and the aqueous phase was extracted with 2 x 200 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (60:40 diethyl ether/petroleum ether) gave 9.1 g (94%) of alcohol **12** as a yellow oil (1.5:1 mixture of *E*/*Z* isomers): IR (thin film) 3346, 3065, 3003, 2938, 1592, 1572, 1493, 1462, 1440, 1406, 1287, 1245, 1174, 1086, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.26 (m, 2H, Ar-H *E* and *Z*), 6.91-6.84 (m, 2H, Ar-H *E* and *Z*), 6.37 (d, J = 14.9 Hz, 0.6H, H-3 *E*), 6.25 (d, J = 9.5 Hz, 0.4H, H-3 *Z*), 5.83 (dt, J = 9.5, 6.3 Hz, 0.4H, H-2 *Z*), 5.70 (dt, J = 14.9, 5.8 Hz, 0.6H, H-2 *E*), 4.34 (d, J = 6.3 Hz, 0.4H, H-1 *Z*), 4.13 (d, J = 5.8 Hz, 0.6H, H-1 *E*), 3.80 (s, 1.8H, OCH_3 *E*), 3.79 (s, 1.2H, OCH_3 *Z*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.4 (C-4' *E*), 159.1 (C-4' *Z*), 133.5 (C-2', C-6' *E*), 132.1 (C-2', C-6' *Z*), 128.5 (C-3 *Z*), 128.2 (C-3 *E*), 127.7 (C-2 *Z*), 127.5 (C-2 *E*), 125.8 (C-1' *Z*), 124.0 (C-1' *E*), 114.8 (C-3', C-5' *E* and *Z*), 62.9 (C-1 *E*), 59.4 (C-1 *Z*), 55.2 (OCH_3 *E* and *Z*). Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.16. Found: C, 60.93; H, 6.17.

(*E*)-3-(4-Methoxyphenylthio)prop-2-enal 13*E*

IBX oxidation: To a solution of 19.5 g (70 mmol, 1.5 equiv) of iodoxybenzoic acid in 100 mL of DMSO (pre-stirred for 15 min at 20 °C) was added a solution of 9.3 g (47 mmol) of alcohol **12** in 50 mL of THF. After stirring for 30 min at 20 °C, 200 mL of water was added and the resulting precipitate was filtrated, rinsing with diethyl ether. The layers of the filtrate were separated and the aqueous phase was extracted with 2 x 200 mL of

diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (30:70 diethyl ether/petroleum ether) gave 9.0 g (97%) of aldehyde **13** as a yellow oil (1.9:1 mixture of *E/Z* isomers).

To a solution of 9.0 g (46 mmol) of the previous aldehyde in 100 mL of CH_2Cl_2 at 20 °C was added 13 mL (230 mmol, 5.0 equiv) of acetic acid and 38 mL (460 mmol, 10 equiv) of pyridine. After stirring for 12 h, the reaction mixture was washed with 100 mL of water and 150 mL of saturated aqueous $CuSO_4$. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 9.0 g (quantitative) of aldehyde **13** as a 35:1 mixture of *E/Z* isomers[12] (P = 0.65 bar, $T_{initial}$ = 100 °C, gradient of 10 °C/min for 10 min then 30 °C/min, $t_R(E)$ = 12.34 min, $t_R(Z)$ = 12.67 min). Purification by recrystallisation from cyclohexane/isopropyl ether afforded 8.7 g (97%) of aldehyde **13*E*** as a yellow crystalline solid (pure *E*): mp 56-57 °C; IR (CH_2Cl_2) 3010, 2943, 2840, 2726, 1670, 1592, 1561, 1494, 1462, 1442, 1387, 1290, 1251, 1174, 1127, 1029 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.42 (d, *J* = 7.9 Hz, 1H, H-1), 7.64 (d, *J* = 14.9 Hz, 1H, H-3), 7.44-7.26 (m, 2H, Ar-H), 6.98-6.94 (m, 2H, Ar-H), 5.84 (dd, *J* = 14.9, 7.9 Hz, 1H, H-2), 3.85 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.5 (C-1), 161.5 (C-4'), 157.8 (C-3), 135.5 (C-2', C-6'), 126.6 (C-2), 119.5 (C-1'), 115.5 (C-3', C-5'), 55.4 (OCH_3); MS (CI, NH_3) *m/z* 212 ($MH^+ + NH_3$), 195 (MH^+), 140, 122, 108, 87, 72. Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.63; H, 5.22.

Dess-Martin oxidation: To a solution of 1.5 g (7.4 mmol) of alcohol **12** in 70 mL of CH_2Cl_2 was added 6.0 mL (74 mmol, 10 equiv) of pyridine, followed by 4.7 g (11 mmol, 1.5 equiv) of the Dess-Martin periodinane. The resulting suspension was stirred at 20 °C for 30 min and treated with 50 mL of saturated aqueous $NaHSO_3$, 50 mL of saturated aqueous $NaHCO_3$ and 100 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with 3 x 100 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (30:70 diethyl ether/petroleum ether) gave 1.13 g (78%) of aldehyde **13*E*** as a yellow crystalline solid (pure *E*). Chromatographic and spectroscopic data are identical to those of the above aldehyde.

Ethyl (2*R,3*S**,3*R**,4*E*)-3-Hydroxy-5-(4-methoxyphenylthio)-2-methylpent-4-enoate**

To a solution of 7.2 mL (51 mmol, 2.4 equiv) of diisopropylamine in 25 mL of THF at -78 °C was added 30 mL (49 mmol, 2.3 equiv) of 1.6 M butyllithium in hexane. After stirring for 30 min, 5.4 mL (47 mmol, 2.2 equiv) of ethyl propionate was added and the resulting solution was stirred at -78 °C for 30 min, and treated with a solution of 4.1 g (21 mmol) of aldehyde **13*E*** in 25 mL of THF (rinse 2 x 25 mL of THF). The reaction mixture was stirred at -78 °C for 30 min before it was diluted with 100 mL of diethyl ether and quenched with 100 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with 3 x 100 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (40:60 diethyl ether/petroleum ether) gave 6.1 g (96%) of the desired aldol as a yellow oil (1:1 mixture of diastereomers): IR (thin film) 3484, 2979, 2938, 2904, 2836, 1731, 1592, 1572, 1494, 1462, 1375, 1287, 1248, 1179, 1097, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H, Ar-H), 6.89-6.86 (m, 2H, Ar-H), 6.42 (d, *J* = 15.0 Hz, 0.5H, H-5), 6.41 (d, *J* = 15.1 Hz, 0.5H, H-5), 5.52 (dd, *J* = 15.0, 6.4 Hz, 0.5H, H-4), 5.51 (dd, *J* = 15.1, 5.9 Hz, 0.5H, H-4), 4.41, 4.22 (m, 1H, H-3), 4.15 (q, *J* = 7.0 Hz, 2H, $OC\mathbf{H}_2CH_3$), 3.81, 3.80 (s, 3H, OCH_3), 2.74 (d, *J* = 4.9 Hz, 0.5H, OH), 2.73 (d, *J* = 5.5 Hz, 0.5H, OH), 2.57 (qd, *J* = 7.2, 4.3 Hz, 0.5H, H-2), 2.51 (quint, *J* = 7.2 Hz, 0.5H, H-2), 1.26 (t, *J* = 7.0 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.15 (d, *J* = 7.2 Hz, 3H, CH_3-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 175.2 (C-1), 159.6, 159.5 (C-4'), 133.8, 133.7 (C-2', C-6'), 129.0, 128.3, 127.8 (C-4, C-5), 123.9, 123.7 (C-1'), 114.8 (C-3', C-5'), 74.4, 72.8 (C-3), 60.7 ($O\mathbf{C}H_2CH_3$), 55.3 (OCH_3), 45.5, 44.8 (C-2), 14.2, 14.1 (CH_3-2), 11.4

(OCH_2CH_3); MS (CI, NH_3) *m/z* 296 ($MH^+ + NH_3 - H_2O$), 279 ($MH^+ - H_2O$), 233, 195, 176, 159, 139. Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.73; H, 6.75. Found: C, 60.69; H, 6.92.

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*R,3*R**,4*E*)-3-*tert*-butyldimethylsiloxy-5-(4-methoxyphenylthio)-2-methylpent-4-enoate 15**

To a solution of 120 mg (0.4 mmol) of the above aldol in 5 mL of CH_2Cl_2 at -78 °C was added 70 μL (0.5 mmol, 1.2 equiv) of triethylamine, followed by 100 μL (0.5 mmol, 1.1 equiv) of TBSOTf. The resulting solution was stirred at -78 °C for 30 min. The reaction failing to go to completion, 70 μL (0.5 mmol, 1.2 equiv) of triethylamine was added, followed by 100 μL (0.5 mmol, 1.1 equiv) of TBSOTf and the reaction mixture was stirred at -78 °C for 30 min. It was then quenched with 10 mL of saturated aqueous NH_4Cl, and the layers were separated. The aqueous phase was extracted with 3 x 10 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (20:80 diethyl ether/petroleum ether) gave 131 mg (78%) of silyl ether **14** as a yellow oil (1:1 mixture of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 6.28, 6.25 (2d, *J* = 15.0 Hz, 1H, H-5), 5.54, 5.41 (2dd, *J* = 15.0, 7.5 Hz, 1H, H-4), 4.40, 4.28 (2t, *J* = 7.5 Hz, 1H, H-3), 4.11-4.05 (m, 2H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 2.51-2.41 (m, 1H, H-2), 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.14, 1.03 (2d, *J* = 7.2 Hz, 3H, CH_3-2), 0.86, 0.83 (2s, 9H, $SiC(CH_3)_3$), 0.02 (s, 6H, $Si(CH_3)_2$).

To a solution of 43 mg (0.1 mmol) of ester 14 in 5 mL of methanol was added 1 mL of 40% aqueous KOH. The resulting mixture was stirred at 20 °C for 2 days, and was then treated with 25 mL of diethyl ether and 25 mL of water. The layers were separated and the aqueous phase was acidified to pH 2 with 4 N aqueous HCl. It was then extracted with 3 x 25 mL of diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give 40 mg of the desired acid as a yellow oil (1:1 mixture of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H, Ar-H), 6.87-6.84 (m, 2H, Ar-H), 6.32-6.29 (m, 1H, H-5), 5.12-4.97 (m, 1H, H-4), 4.45-4.33 (m, 1H, H-3), 3.77 (s, 3H, OCH_3), 2.59-2.48 (m, 1H, H-2), 1.12, 1.06 (2d, *J* = 8.0 Hz, 3H, CH_3-2), 0.88-0.84 (m, 9H, $SiC(CH_3)_3$), 0.06-0.02 (m, 6H, $Si(CH_3)_2$).

To a solution of 40 mg (0.1 mmol) of the above unpurified acid and 12 mg (0.1 mmol) of (*E*)-methyl 4-hydroxycrotonate in 2 mL of CH_2Cl_2 was added 24 mg (0.12 mmol, 1.2 equiv) of DCC, followed by a catalytic amount of DMAP. The cloudy mixture was stirred at 20 °C for 30 min, diluted with petroleum ether, and then filtered through cotton, rinsing with petroleum ether. The filtrate was partitioned between 10 mL of diethyl ether and 10 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was extracted with 3 x 10 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (10:90, 20:80 diethyl ether/petroleum ether) gave 32 mg (64% for two steps) of ester **15** as a yellow oil (1:1 mixture of diastereomers): IR (thin film) 2952, 2856, 2360, 2341, 1728, 1667, 1593, 1494, 1462, 1436, 1286, 1247, 1172, 1104, 1065, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H, Ar-H), 6.93 (dt, *J* = 15.8, 4.6 Hz, 1H, H-2'), 6.89-6.86 (m, 2H, Ar-H), 6.29, 6.27 (2d, *J* = 15.1 Hz, 1H, H-5), 6.03 (d, *J* = 15.8 Hz, 1H, H-3'), 5.50 (dd, *J* = 15.1, 7.0 Hz, 0.5H, H-4), 5.36 (dd, *J* = 15.1, 7.8 Hz, 0.5H, H-4), 4.71-4.68 (m, 2H, H_2-1'), 4.42 (t, *J* = 7.0 Hz, 0.5H, H-3), 4.28 (t, *J* = 7.8 Hz, 0.5H, H-3), 3.81, 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.57-2.52 (m, 1H, H-2), 1.15, 1.05 (2d, *J* = 7.8 Hz, 3H, CH_3-2), 0.84, 0.82 (2s, 9H, $SiC(CH_3)_3$), 0.01 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 166.3 (C-1, C-4'), 159.8, 159.7 (C-4"), 141.5 (C-3'), 134.1, 133.8 (C-2", C-6"), 129.8, 129.1, 128.8, 127.6 (C-4, C-5), 124.1, 123.8 (C-1"), 122.0 (C-2'), 115.0, 114.9 (C-3", C-5"), 75.9, 74.8 (C-3), 62.6 (C-1'), 55.5 (Ar-OCH_3), 51.8 (OCH_3), 47.3, 47.1 (C-2), 25.8 ($SiC(CH_3)_3$), 18.2, 18.1 ($SiC(CH_3)_3$), 13.4, 11.9 (CH_3-2),

-3.9, -4.0, -5.0 ($Si(CH_3)_2$); MS (CI, NH_3) *m/z* 498 ($MH^+ + NH_3$), 350, 349, 309, 233.

Methyl (2*E*)-4-(2-Bromopropionyloxy)but-2-enoate 16

To a solution of 9.2 g (79 mmol) of methyl 4-hydroxycrotonate in 150 mL of CH_2Cl_2 at 20 °C was added 10.5 mL (130 mmol, 1.65 equiv) of pyridine, followed by 12.3 mL (117 mmol, 1.48 equiv) of 2-bromopropionyl bromide. The resulting solution was stirred at 20 °C for 10 min and treated with 500 mL of water and 450 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with 2 x 500 mL of diethyl ether. The combined organic layers were washed with brine, saturated aqueous $CuSO_4$, water, and saturated aqueous $NaHSO_3$, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (30:70 diethyl ether/petroleum ether) gave 17.4 g (88%) of ester **16** as a colorless oil: IR (thin film) 2994, 2953, 1738, 1737, 1440, 1381, 1313, 1279, 1218, 1156, 1075, 1041 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.87 (dt, *J* = 15.8, 4.5 Hz, 1H, H-3), 5.80 (dt, *J* = 15.8, 1.8 Hz, 1H, H-2), 4.22 (dt, *J* = 4.5, 1.8 Hz, 2H, H-4), 3.71 (q, *J* = 4.5 Hz, 1H, H-2'), 2.88 (s, 3H, OCH_3), 0.50 (d, *J* = 6.9 Hz, H_3-3'); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7, 166.2 (C-1, C-1'), 140.5 (C-3), 122.5 (C-2), 63.8 (C-4), 51.2 (OCH_3), 39.5 (C-2'), 21.7 (C-3'); MS (CI, NH_3) *m/z* 270/268 ($MH^+ + NH_3$), 253/251 (MH^+), 116, 101/99, 71. Anal. Calcd for $C_8H_{11}O_4Br$: C, 38.26; H, 4.41. Found: C, 38.31; H, 4.31.

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*R*S,3*R**,4*E*)-3-Hydroxy-5-(4-methoxyphenylthio)-2-methylpent-4-enoate 17**

A suspension of 3.5 g (18 mmol) of aldehyde **13*E***, 2.4 g (36 mmol, 2.0 equiv) of zinc dust, and 5.0 g (20 mmol, 1.1 equiv) of bromide **16** in 50 mL of THF was sonicated for 1 h at 55 °C. It was then filtered, rinsing with diethyl ether, and the filtrate was partitioned between 50 mL of iced water and 50 mL of diethyl ether. The layers were separated and the aqueous phase was extracted with 2 x 500 mL of diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (40:60, 50:50, 60:40, 70:30, 80:20, 90:10, 100:0 diethyl ether/petroleum ether) gave 4.8 g (67%) of aldol **17** as a yellow oil (1.5:1 mixture of diastereomers): IR (thin film) 3488, 2948, 2837, 1725, 1665, 1592, 1571, 1494, 1457, 1437, 1384, 1286, 1246, 1173, 1100, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H, Ar-H), 6.92 (dt, *J* = 15.7, 4.6 Hz, 1H, H-2'), 6.88-6.85 (m, 2H, Ar-H), 6.42 (d, *J* = 14.8 Hz, 1H, H-5), 6.07-6.00 (m, 1H, H-3'), 5.52 (dd, *J* = 14.8, 6.3 Hz, 0.4H, H-4), 5.47 (dd, *J* = 14.8, 7.3 Hz, 0.6H, H-4), 4.80-4.73 (m, 2H, H-1'), 4.46-4.43 (m, 0.4H, H-3), 4.28-4.23 (m, 0.6H, H-3), 3.80 (s, 1.8H, OCH_3), 3.79 (s, 1.2H, OCH_3), 3.74 (s, 1.2H, OCH_3), 3.73 (s, 1.8H, OCH_3), 2.66-2.61 (m, 0.4H, H-2), 2.59-2.54 (m, 0.6H, H-2), 1.18, 1.15 (2d, *J* = 7.1 Hz, 3H, CH_3-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 166.2 (C-1, C-1'), 159.8, 159.7 (C-4"), 141.2, 141.1 (C-2'), 134.0, 133.8 (C-2", C-6"), 129.8, 128.8 (C-4, C-5), 128.0, 127.7 (C-1"), 122.2, 122.1 (C-3'), 115.0, 114.9 (C-3", C-5"), 75.5, 72.9 (C-3), 62.7 (C-1'), 55.4 ($ArOCH_3$), 51.7 (OCH_3), 45.8, 45.1 (C-2), 14.0, 11.4 (CH_3-2); MS (CI, NH_3) *m/z* 384 ($MH^+ + NH_3$), 366 ($MH^+ + NH_3 - H_2O$), 349 ($MH^+ - H_2O$), 244, 207, 195, 139, 125, 87, 71, 55. Anal. Calcd for $C_{18}H_{22}O_6S$: C, 59.00; H, 6.05. Found: C, 59.05; H, 5.92.

(2*E*)-3-Methoxycarbonylprop-2-enyl (4*E*)-5-(4-Methoxyphenylthio)-2-methyl-3-oxopent-4-enoate 7b

To a solution of 1.0 g (2.7 mmol) of alcohol **17** in 20 mL of CH_2Cl_2 at 20 °C was added 770µl (9.6 mmol, 3.5 equiv) of pyridine, followed by 1.2 g (2.7 mmol, 1.0 equiv) of the Dess-Martin periodinane. After stirring for 1 h at 20 °C, 10 mL of CH_2Cl_2 was added, followed by 330 µl (4.1 mmol, 1.5 equiv) of pyridine, and 1.2 g (2.7 mmol, 1.0 equiv) of periodinane. The resulting mixture was stirred at 20 °C for 1 h and sequentially treated with 25 mL of saturated aqueous $NaHSO_3$ and 25 mL of saturated aqueous $NaHCO_3$. The

two-phase mixture was filtered, rinsing with 50 mL of petroleum ether. The layers were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic layers were washed with saturated aqueous $CuSO_4$, water, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (40:60, 50:50, 60:40, 70:30 diethyl ether/petroleum ether) gave 660 mg (66%) of ketone **7b** as a yellow oil (10:1 ketone/enol as determined by ^1H NMR, only the ketone form is described): IR (thin film) 2948, 2840, 1728, 1668, 1592, 1556, 1495, 1436, 1379, 1250, 1174, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 14.8 Hz, 1H, H-5), 7.44-7.39 (m, 2H, Ar-H), 6.96-6.94 (m, 2H, Ar-H), 6.90 (dt, *J* = 15.7, 5.0 Hz, 1H, H-2'), 6.00 (dt, *J* = 15.7, 1.8 Hz, 1H, H-3'), 5.98 (d, *J* = 14.8 Hz, 1H, H-4), 4.75-4.74 (m, 2H, H-1'), 3.84, 3.75 (2s, 6H, OCH_3), 3.63 (q, *J* = 7.0 Hz, 1H, H-2), 1.34 (d, *J* = 7.0 Hz, 3H, CH_3-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.0 (C-3), 169.9, 166.1 (C-1, C-1'), 161.0 (C-4"), 150.5 (C-2'), 140.8 (C-5), 135.2 (C-2", C-6"), 122.3 (C-3'), 120.7 (C-4), 120.2 (C-1"), 115.5 (C-3", C-5"), 62.5 (C-1'), 55.4 ($ArOCH_3$), 51.6 (OCH_3), 51.1 (C-2), 13.1 (CH_3-2); MS (CI, NH_3) *m/z* 382 ($MH^+ + NH_3$), 365 (MH^+), 267, 242, 223, 193, 116. Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53. Found: C, 59.27; H, 5.79.

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*E*,4*E*)-3-*tert*-Butyldimethylsiloxy-5-(4-methoxyphenylthio)-2-methylpenta-2,4-dienoate 19*E*

To a solution fo 200 mg (0.6 mmol) of ketoester **7b** in 6 mL of CH_2Cl_2 ar 20 °C was added 150 µl (1.2 mmol, 2.0 equiv) of triethylamine, followed by 150 µl (0.7 mmol, 1.2 equiv) of TBSOTf. The reaction mixture was stirred at 20 °C for 3 days and partitioned between 20 mL of saturated aqueous $NaHCO_3$ and 40 mL of petroleum ether. The layers were separated and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (30:70 diethyl ether/petroleum ether) gave 120 mg (46%) of pure silyl enol ether **19*E*** as a yellow crystalline solid: mp 141-142 °C; IR ($CDCl_3$) 3154, 2954, 2932, 2899, 2860, 1816, 1793, 1721, 1668, 1592, 1551, 1494, 1470, 1438, 1382, 1288, 1247, 1200, 1174, 1097, 1070, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H, Ar-H), 7.23 (d, *J* = 15.1 Hz, 1H, H-5), 6.96 (dt, *J* = 15.7, 4.4 Hz, 1H, H-2'), 6.91-6.89 (m, 2H, Ar-H), 6.85 (d, *J* = 15.1 Hz, 1H, H-4), 5.99 (dt, *J* = 15.7, 1.9 Hz, 1H, H-3'), 4.73-4.72 (m, 2H, H-1'), 3.82, 3.75 (2s, 6H, OCH_3), 1.88 (s, 3H, CH_3-2), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.13 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.1 (C-1, C-1'), 160.0 (C-4"), 142.3 (C-2'), 135.5 (C-5), 134.5 (C-2", C-6"), 133.0 (C-3), 123.0 (C-1"), 121.6 (C-4), 121.3 (C-3'), 115.0 (C-3", C-5"), 108.6 (C-2), 62.2 (C-1'), 55.4 ($ArOCH_3$), 51.7 (OCH_3), 25.9 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), 13.9 (CH_3-2), -3.2, -3.8 ($Si(CH_3)_2$); MS (CI, NH_3) *m/z* 479 (MH^+), 382, 365, 339, 267, 241, 223. Anal. Calcd for $C_{24}H_{34}O_6SSi$: C, 60.21; H, 7.16. Found: C, 59.89; H, 7.02.

Methyl (3a*R,4*S**,5*S**,7a*R**)-5-(4-Methoxyphenylthio)-7a-methyl-1-oxo-7-*tert*-butyldimethylsiloxy-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylate 21**

A solution of 120 mg (0.25 mmol) of silyl enol ether **19*E*** in 5 mL of toluene was refluxed for 6 days. The solvent was then evaporated *in vacuo*. Purification by flash-chromatography on silica gel (20:80 diethyl ether/petroleum ether) afforded 28 mg (23%) of bicyclic compound **21** as a yellow crystalline solid: mp 124-125 °C; IR (CCl_4) 3001, 2953, 2931, 2858, 2837, 1782, 1741, 1654, 1591, 1551, 1493, 1471, 1463, 1437, 1405, 1382, 1362, 1345, 1286, 1244, 1220, 1205, 1152, 1090, 1071, 1048, 1036, 1020, 1007 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, taxol numbering) δ 7.37-7.34 (m, 2H, Ar-H), 6.83-6.81 (m, 2H, Ar-H), 5.04 (d, *J* = 6.1 Hz, 1H, H-6), 4.39 (dd, *J* = 10.2, 5.5 Hz, 1H, H-2), 4.06 (dd, *J* = 6.1, 4.6 Hz, 1H, H-5), 3.99 (d, *J* = 10.2 Hz, 1H, H-2), 3.79, 3.48 (2s, 6H, OCH_3), 2.95 (dd, *J* = 12.7, 4.6 Hz, 1H, H-4), 2.76 (dd, *J* = 12.7, 5.5 Hz, 1H, H-3), 1.14 (s, 3H, CH_3-8), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.24, 0.22 (2s, 6H, $Si(CH_3)_2$);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (C-9), 171.4 (CO-4), 160.0 (C-4'), 150.6 (C-7), 137.3 (C-2', C-6'), 123.5 (C-1'), 114.2 (C-3', C-5'), 103.4 (C-6), 69.0 (C-2), 55.4 ($ArOCH_3$), 51.8 (OCH_3), 46.6, 46.1 (C-4, C-5), 45.5 (C-8), 40.5 (C-3), 25.7 ($SiC(CH_3)_3$), 20.1 (CH_3-8), 18.2 ($SiC(CH_3)_3$), -4.3, -5.0 ($Si(CH_3)_2$); MS (CI, NH_3) *m/z* 479 (MH^+), 356, 339, 242, 132, 78. Anal. Calcd for $C_{24}H_{34}O_6SSi$: C, 60.21; H, 7.16. Found: C, 59.81; H, 7.08.

(2*E*)-3-Methoxycarbonylprop-2-enyl (2*E*)-3-*tert*-Butyldimethylsiloxy-2-methylpenta-2,4-dienoate 22*E*

To a solution of 221 mg (0.98 mmol) of ketoester **7a** in 10 mL of diethyl ether was added 340 µL (2.4 mmol, 2.5 equiv) of triethylamine, followed by 295 mg (1.95 mmol, 2.00 equiv) of TBSCl and a few crystals of DMAP. The resulting suspension was stirred at 20 °C for 16 h, and was partitioned between 50 mL of petroleum ether and 50 mL of saturated aqueous $NaHCO_3$. The layers were separated and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash-chromatography on silica gel (10:90 diethyl ether/petroleum ether) gave 278 mg (50%) of silyl enol ether **22*E*** as a white crystalline solid: mp 27-28 °C; IR ($CDCl_3$) 2954, 2931, 1860, 1720, 1667, 1624, 1568, 1463, 1438, 1406, 1286, 1259, 1199, 1177, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 17.2, 11.0 Hz, 1H, H-4), 7.00 (dt, *J* = 15.7, 4.4 Hz, 1H, H-2'), 6.05 (dt, *J* = 15.7, 2.0 Hz, 1H, H-3'), 5.64 (dd, *J* = 17.2, 1.7 Hz, 1H, H-5*trans*), 5.35 (dd, *J* = 11.0, 1.7 Hz, 1H, H-5*cis*), 4.79 (dd, *J* = 4.4, 2.0 Hz, 2H, H-1'), 3.75 (s, 3H, OCH_3), 1.92 (s, 3H, CH_3-2), 1.01 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.4 (C-1, C-4'), 158.9 (C-3), 142.1 (C-2'), 132.3 (C-4), 120.7 (C-5), 119.8 (C-3'), 111.3 (C-2), 62.4 (C-1'), 51.7 (OCH_3), 25.9 ($SiC(CH_3)_3$), 18.6 ($SiC(CH_3)_3$), 13.9 (CH_3-2), -3.4 ($Si(CH_3)_2$). Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 59.96; H, 8.29. Found: C, 59.93; H, 8.21.

Methyl (3a*R,4*S**,7a*R**)-7-*tert*-Butyldimethylsiloxy-7a-methyl-1-oxo-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-carboxylate 23**

A solution of 30.0 mg (0.09 mmol) of silyl enol ether **22*E*** in 10 mL of toluene was refluxed for 4 days. The solvant was then evaporated *in vacuo*. Purification by flash-chromatography on silica gel (20:80, 50:50 diethyl ether/petroleum ether) afforded 18.0 mg (51%) of the starting silyl enol ether and 17.0 mg (49%) of bicyclic compound **23** as a white crystalline solid: mp 76-77 °C; IR ($CDCl_3$) 2949, 2892, 2857, 1780, 1736, 1663, 1490, 1462, 1390, 1297, 1232, 1206, 1175, 1098, 1083, 1043, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, taxol numbering) δ 4.85 (t, *J* = 4.1 Hz, 1H, H-6), 4.38 (dd, *J* = 9.5, 6.2 Hz, 1H, H-2), 4.01 (dd, *J* = 9.5, 3.8 Hz, 1H, H-2), 3.72 (s, 3H, OCH_3), 2.73 (ddd, *J* = 9.7, 6.2, 3.8 Hz, 1H, H-3), 2.60 (dd, *J* = 7.0, 4.1 Hz, 1H, H-5), 1.43 (s, 3H, CH_3-8), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.20, 0.18 (2s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$, taxol numbering) δ 176.3 (C-9), 174.1 (CO-4), 147.8 (C-7), 101.0 (C-6), 68.2 (C-2), 52.1 (OCH_3), 45.5 (C-8), 44.5 (C-4), 39.3 (C-3), 25.7 ($SiC(CH_3)_3$), 24.7 (C-5), 20.6 (CH_3-8), 18.2 ($SiC(CH_3)_3$), -4.4, -4.9 ($Si(CH_3)_2$). Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 59.96; H, 8.29. Found: C, 59.98; H, 8.27.

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REFERENCES AND NOTES

1 a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327. b) ACS Symposium Series 583, *Taxane Anticancer Agents : Basic Science and Current Status*; Georg, G.I.; Chen, T.T.; Ojima, I.; Vyas, D.M., Eds.; American Chemical Society, Washington D.C., 1995.

2 Lavelle F.; Guéritte-Voegelein, F.; Guénard, D. *Bull. Cancer* **1993**, *80*, 326-338. Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160-167 and references cited therein.

3 See Ref. 1b); Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15-44. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47-75. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1-206. Swindell, C. S. *Stud. Nat. Prod. Chem.* **1993**, *12*, 179-231. Paquette, L. A. *Stud. Nat. Prod. Chem.* **1992**, *11*, 3-69. Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52* , 1-34. Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465-543.

4 a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *ibid.* **1995**, *117*, 634-644. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *ibid.* **1995**, *117*, 645-652. Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *ibid.* **1995**, *117*, 653-659. b) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang., P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang., P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *ibid.* **1994**, *116*, 1599-1600. c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723-1726. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755-2756; Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

5 Muller, B.; Delaloge, F.; den Hartog, M.; Férézou, J.-P.; Pancrazi, A.; Prunet, J.; Lallemand, J.-Y.; Neuman, A.; Prangé, T. *Tetrahedron Lett.* **1996**, *37*, 3313-3316; Delaloge, F.; Prunet, J.; Pancrazi, A.; Lallemand, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 237-240.

6 Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Chem. Soc., Perkin Trans. I* **1992**, 2527-2535.

7 Smith III, A. B.; Levenberg, P. A. *Synthesis* **1981**, 567-570.

8 Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866-3869. The yield of methyl 4-bromocrotonate hydrolysis can be improved from 51% to 82% if a standard extraction is performed.

9 The *E*/*Z* ratio was determined by ^{1}H NMR.

10 Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156; Dess, D. B.; Martin, J. C. *J. Am.*

Chem. Soc. **1991**, *113*, 7277-7287; Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

11 IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019-8022; Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272-7276.

12 The *E*/*Z* ratio was determined by GC on SGE 250 QC3/BP5 0.5 capillary column.

13 For a review, see: Fürstner, A. *Synthesis* **1989**, 571-590.

14 Gilbert, J. C.; Kelly, T. A. *Tetrahedron* **1988**, *44*, 7587-7600.

15 Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465-468.

16 The *E*/*Z* ratio was determined by 1H NMR and the stereochemistry of the silyl enol ethers by NOESY NMR experiments.

17 Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274-3276.

18 The reaction was slow in dichloromethane, and the ketoester tended to polymerize in DMF in the presence of triethylamine.

19 For the influence of a methyl group in such a position in an IMDA reaction, see: Tahri, A.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1994**, *35*, 3945-3948.

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