

## STEREOSELECTIVE TOTAL SYNTHESIS OF SYRIBUTINS 1 AND 2

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## ABSTRACT

A novel protocol for the generation of  $\beta$ -branched Baylis-Hillman adducts in moderate yields (52–68%) as *E/Z* mixtures from commercially available dienoates such as ethyl sorbate and aryl aldehydes catalyzed by DABCO in DMSO.

**Keywords:** Baylish-Hillmann reaction, DABCO, Syributins, *E/Z* mixtures

## INTRODUCTION

The modern synthetic organic chemistry is aptly referred to as a form of “art and architecture”, since it requires skill and creativity. This art is a powerful tool in the hands of a chemist who is an artist of schemes and an architect of molecules, in the pursuit of understanding, imitating and conquering “the nature” and its stupefying natural biological processes.

Having advanced instrumental techniques along with a vast number of synthetic reagents and other operational and technical facilities at his disposal, chemist is doing away with traditional techniques of resolution in synthetic schemes and started devising schemes that utilize available and operationally versatile optically active starting materials and reagents.

This development has broadly divided the modern synthetic organic chemistry into two inter-related yet independent branches, the “asymmetric synthesis”, in which the emphasis is on chiral reagents, and the “Chiron approach” in which starting materials are optically active. The evolution of asymmetric synthesis is unpredictable, but the dramatic progress will certainly persist. It appears as if we have entered an era of optically active reagents with astounding inherent prochiral free selectivity. The beauty and power of many of these new reagents lie in their capacity to move us beyond the influence of existing chiral centers in substrates to a very high predictable control of stereoselectivity.

## MATERIAL AND METHODS

**General:** - Melting points were determined on a Polmon instrument (model no. MP 96). IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and  $^1\text{H}$  NMR (200 MHz) and  $^{13}\text{C}$  NMR (50 MHz) were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass 70-70H instrument.

**i. General procedure for the synthesis Ethyl 2-[[[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]acrylate (2)**

Aldehyde **1** (4.0 g, 30.8 mmol) in 1,4 dioxane:water [(1:1), 30 mL] was treated with ethyl acrylate (6.7 mL, 61.5 mmol) in presence of DABCO (3.5 g, 30.8 mmol) at room temperature for 24 h. Then the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3  $\times$  20 mL). The combined organic layers was washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to get a residue, which was purified by chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 1.5:8.5) to afford **2** (5.1 g, 72%) as a light yellow liquid with 80% *de*.  $[\alpha]_{\text{D}} -6.4$  (c 1,  $\text{CHCl}_3$ ); IR (neat): 1668, 1730, 3395  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.32-1.38 (s, 6H, 2x- $\text{CH}_3$ ), 1.45 (s, 3H, - $\text{CH}_3$ ), 2.94 (d, 1H,  $J = 4.5$  Hz, -OH), 3.91 (d, 2H,  $J = 7.5$  Hz, H-5, H-5'), 4.23-4.38 (m, 3H, - $\text{OCH}_2$ , H-4), 4.5 (dd, 1H,  $J = 4.5$ , 10.4 Hz, H-3), 5.99 (s, 1H, olefinic), 6.36 (s, 0.9H, olefinic), 6.38 (s, 0.1H, olefinic).

ESIMS: 215 ( $\text{M}^+ - 15$ );

**ii. 1-[[[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylene-1,3-propanediol (3)**

To a cooled (0  $^\circ\text{C}$ ) and stirred suspension of  $\text{LiAlH}_4$  (1.1 g, 30.3 mmol) in dry ether (10 mL), a solution of  $\text{AlCl}_3$  (1.34 g, 10.1 mmol) in dry ether was added slowly and stirred for 30 min at 0  $^\circ\text{C}$  then a solution of **2** (4.6 g, 20.2 mmol) in dry ether (25 mL) was added dropwise and stirred for 2 h at 0  $^\circ\text{C}$ . The reaction mixture was quenched with sat. aq.  $\text{Na}_2\text{SO}_4$  solution (20 mL) at 0  $^\circ\text{C}$  then EtOAc (60 mL) was added and stirred the reaction mixture for an additional 30 min at room temperature. The mixture was filtered through celite and washed with EtOAc (3  $\times$  50 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure and the residue purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 1.5:3.5) to afford **3** (2.58 g, 68%) as a light yellow syrup. IR (neat): 2940, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H, - $\text{CH}_3$ ), 1.45 (s, 3H, - $\text{CH}_3$ ), 3.88-4.06 (m, 2H, H-5, 5'), 4.12-4.28 (m, 4H, H-1, 1', H-3, H-4), 5.21 (br. s, 2H, olefinic).

ESIMS: 189 ( $\text{M}^+ + 1$ );

**iii. 2-[[[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]allyl acrylate (4)**

To a stirred and cooled (0  $^\circ\text{C}$ ) solution of alcohol **3** (2.4 g, 12.60 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (50 mL), *N*- ethyldiisopropylamine (3.3 mL, 18.90 mmol) followed by acryloyl chloride (1.04 mL, 12.60 mmol), were added at 0  $^\circ\text{C}$  and stirred for room temperature for 10 h. After the completion of the reaction, reaction mixture was quenched with sat.  $\text{NaHCO}_3$  (15 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  25 mL). The combined organic layers were washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure and the obtained residue was purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 1:4) to afford **4** (2.3 g, 75%) as a light yellow syrup. IR (neat): 1725, 2935, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H, - $\text{CH}_3$ ), 1.45 (s, 3H, - $\text{CH}_3$ ), 3.78-3.95 (m, 2H, H-5, 5'), 4.13-4.22 (m, 1H, H-4), 4.29 (d, 1H,  $J = 3.68$  Hz, H-3), 4.7 (s, 1.8H, H-1, 1'), 4.72 (s, 0.2H, H-1, 1'), 5.29 (s, 1H, olefinic), 5.39 (s, 1H, olefinic), 5.85 (dd, 1H,  $J = 1.51$ , 10.57 Hz, olefinic), 6.15 (dd, 1H,  $J = 10.57$ , 17.37 Hz, olefinic), 6.43 (dd, 1H,  $J = 1.51$ , 17.37 Hz, olefinic).

ESIMS: 243 ( $\text{M}^+ + 1$ );

**iv. 4-(R)-1-[[[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-hydroxymethyl-2,5-dihydro-2-furanone (5)**

To a stirred solution of ester **4** (0.25 g, 1.03 mmol) in dry  $\text{CH}_2\text{Cl}_2$ , Grubbs' 1<sup>st</sup> generation catalyst (0.085 g, 0.103 mmol) was added and heated at reflux for 2 days under Ar. After the completion of the reaction crude reaction mixture was concentrated under reduced pressure to get a residue, which was purified by chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 20:80 to 40:60) to allow the separation of the desired isomer **5** (0.014 g) from undesired derivative **5** (0.12 g) (combined yield 62%).  $[\alpha]_{\text{D}} -12.7$  (c 0.6,  $\text{CHCl}_3$ );

IR (neat): 1720, 3050  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H, - $\text{CH}_3$ ), 1.45 (s, 3H, - $\text{CH}_3$ ), 2.78 (br.s, 1H, -OH), 3.87 (dd, 1H,  $J = 5.9, 8.8$  Hz, H-5), 4.06 (dd, 1H,  $J = 6.6, 8.0$  Hz, H-5'), 4.18 (q, 1H,  $J = 5.86$  Hz, H-4), 4.51 (d, 1H,  $J = 3.66$  Hz, H-3), 4.87 (br.s, 2H, H-1, 1'), 6.01 (s, 1H, olefinic);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.79, 26.38, 65.66, 69.15, 71.6, 96.12, 110.42, 116.30, 168.44, 173.16; FABMS ( $m/z$ , %): 215 ( $M^+$ , 16), 149 (27), 69 (60), 55 (100).

**v.4-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]carbonyl-2,5-dihydro-2-furanone (6)**

To a stirred solution of **5** (0.12 g, 0.56 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was added PDC (0.422 g, 1.12 mmol) and stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 1:4) to obtain **6** (0.113 g, 95%) as a colorless liquid. IR (neat): 1670, 1720, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.40 (s, 6H, 2 x - $\text{CH}_3$ ), 4.18-4.30 (m, 2H, H-5, 5'), 4.78 (d, 1H,  $J = 5.20$  Hz, H-4), 5.02 (s, 2H, H-1, 1'), 6.93 (s, 1H, olefinic).

ESIMS: 213 ( $M^+$ +1);

**vi.(R)-1-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(5-oxo-2,5-dihydro-3-furanyl)methyl hexanoate (7)**

To a stirred and cooled (0  $^\circ\text{C}$ ) solution of alcohol **5** (0.1 g, 0.467 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2 mL),  $\text{Et}_3\text{N}$  (0.13 mL, 0.93 mmol) followed by hexanoyl chloride (0.078 mL, 0.56 mmol), were added at 0  $^\circ\text{C}$  and stirred for room temperature for 0.5 h. After the completion of the reaction, reaction mixture was quenched with sat.  $\text{NaHCO}_3$  (1 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 5 mL). The combined organic layers were washed with  $\text{H}_2\text{O}$  (4 mL), brine (4 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure and the obtained residue was purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 1:4) to afford **7** (0.127 g, 87%) as a light yellow syrup. IR (neat): 1725, 1745, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.93 (t, 3H,  $J = 6.8$  Hz, - $\text{CH}_3$ ), 1.24-1.32 (m, 7H, 2x- $\text{CH}_2$ ), 1.35 (s, 3H, - $\text{CH}_3$ ), 1.60-1.69 (m, 2H, - $\text{CH}_2$ ), 2.38 (t, 2H,  $J = 7.4$  Hz, - $\text{CH}_2$ ), 3.74-3.81 (m, 1H, H-5), 4.02-4.13 (m, 1H, H-5'), 4.29-4.38 (m, 1H, H-4), 4.90 (ddd, 2H,  $J = 1.1, 1.6, 17.9$  Hz, H-1, 1'), 5.78 (d, 1H,  $J = 3.68$  Hz, H-3), 6.05 (s, 1H, olefinic);

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.84, 22.25, 24.53, 29.70, 31.25, 34.07, 64.82, 68.87, 71.60, 116.85, 169.08, 173.33, 174.53;

ESIMS: 313 ( $M^+$ +1).

**vii.(2R,3R)-2,3-Dihydroxy-3-(5-oxo-2,5-dihydro-3-furanyl)propyl hexanoate (8a)**

PTSA (0.024 g, 0.14 mmol) was added to a stirred solution of **7** (0.11 g, 0.35 mmol) in methanol (2 mL) and stirred at room temperature for 2 h. Reaction mixture was quenched with triethylamine (0.5 mL) stirred for 5 min. The reaction mixture was concentrated and diluted with EtOAc (15 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 2:3) to obtain **8a** (0.086 g, 90%) as a light yellow syrup.  $[\alpha]_D +6.4$  (c 0.4,  $\text{CHCl}_3$ ); IR (neat): 1725, 1745, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.9 (t, 3H,  $J = 7.0$  Hz, - $\text{CH}_3$ ), 1.28-1.35 (m, 4H, 2 x - $\text{CH}_2$ ), 1.62-1.68 (m, 2H, - $\text{CH}_2$ ), 2.36 (t, 2H,  $J = 7.6$  Hz, - $\text{CH}_2$ ), 3.93-3.97 (m, 1H, H-4), 4.18 (dd, 1H,  $J = 6.4, 11.9$  Hz, H-5), 4.33 (dd, 1H,  $J = 5.2, 11.9$  Hz, H-5'), 4.62 (br.s, 1H, H-3), 4.94 (ddd, 2H,  $J = 1.1, 1.6, 17.9$  Hz, H-1, 1'), 6.07 (s, 1H, olefinic).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.84, 22.25, 24.53, 29.70, 31.25, 34.07, 64.82, 68.87, 71.60, 116.85, 169.08, 173.33, 174.53.

FABMS ( $m/z$ , %): 273 ( $M^+$ , 18), 157 (42), 99 (87), 71 (100);

**viii.(2R,3R)-2,3-Dihydroxy-3-(5-oxo-2,5-dihydro-3-furanyl)propyl octanoate (8b)**

PTSA (0.018 g, 0.105 mmol) was added to a stirred solution of **7** (0.09 g, 0.26 mmol) in methanol (2 mL) and stirred at room temperature for 2 h. Reaction mixture was quenched with triethylamine (0.5 mL) stirred for 5 min. The reaction mixture was concentrated and diluted with EtOAc (15 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 60-120 mesh, EtOAc:Hexane, 2:3) to obtain **8b** (0.068 g, 86%) as a light yellow syrup.

$[\alpha]_D +7.4$  (c 0.4,  $\text{CHCl}_3$ ); IR (neat): 1725, 1745, 3050  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.88 (t, 3H,  $J = 6.5$  Hz, - $\text{CH}_3$ ), 1.19-1.28 (m, 8H, 4 x - $\text{CH}_2$ ), 1.58-1.68 (m, 2H, - $\text{CH}_2$ ), 2.30 (t, 2H,  $J = 6.5$  Hz, - $\text{CH}_2$ ), 3.89-3.95 (m, 1H, H-4), 4.13 (dd, 1H,  $J = 5.2, 11.7$  Hz, H-5), 4.21 (dd, 1H,  $J = 5.2, 11.7$  Hz, H-5'), 4.60 (br. s, 1H, H-3), 4.90 (ddd, 2H,  $J = 0.6, 1.8, 17.9$  Hz, H-1, 1'), 6.03 (s, 1H, olefinic).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.02, 22.55, 24.83, 28.80, 29.02, 31.59, 34.07, 64.91, 69.37, 71.99, 72.33, 116.64, 169.27, 173.67, 174.98.

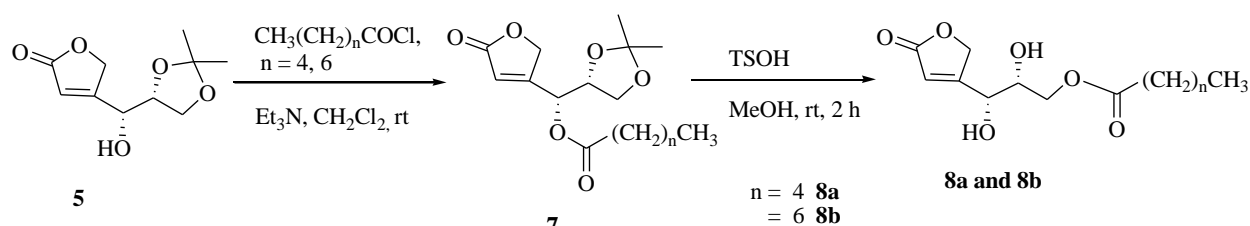
FABMS ( $m/z$ , %): 273 ( $M^+$ , 18), 157 (42), 99 (87), 71 (100);

**RESULT AND DISCUSSIONS:**

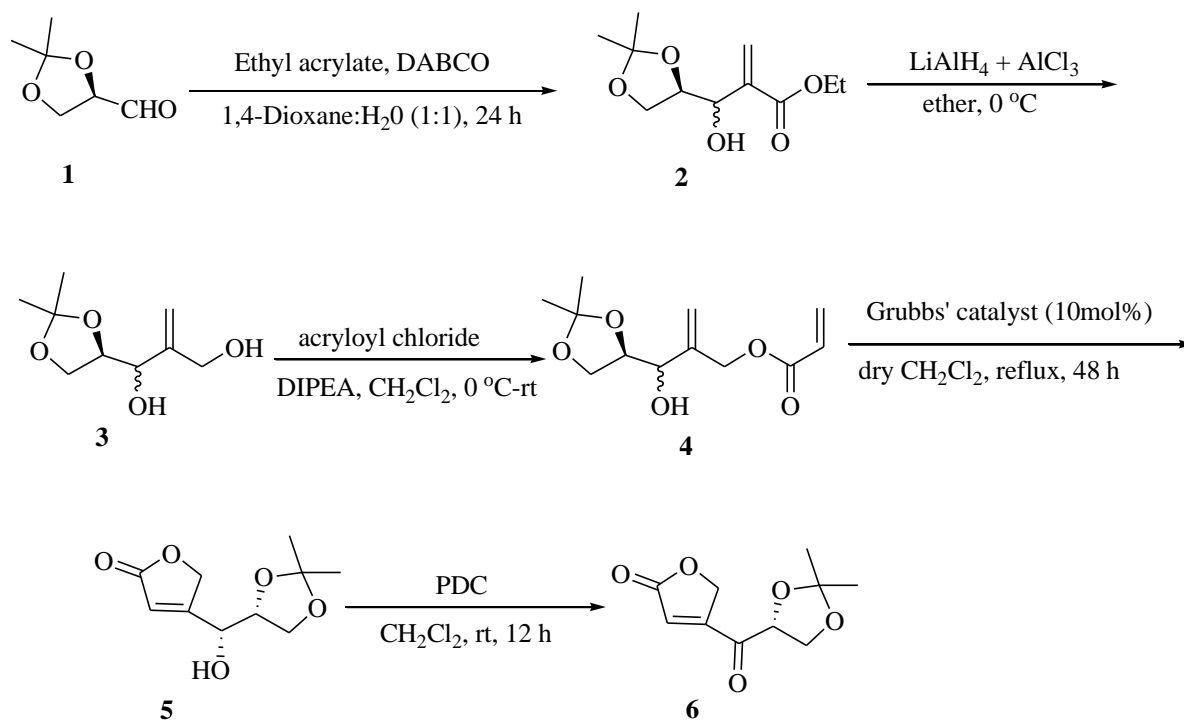
**Synthesis of (2R,3R)-2,3-Dihydroxy-3-(5-oxo-2,5-dihydro-3-furanyl) propyl hexanoate (8a)**

PTSA was added to a stirred solution of **7** in methanol and stirred at room temperature for 2 hours to give (2R,3R)-2,3-Dihydroxy-3-(5-oxo-2,5-dihydro-3-furanyl)propyl hexanoate (**8a**). The  $^1\text{H}$  NMR showed the **8a** and **8b** indicated the disappearance of acetonide protons and down field shift of H-5 protons (about 0.4 ppm, as compared with same proton in compound **7**) at  $\delta$  4.18 ( $J = 6.4, 11.9$  Hz, 1H), at  $\delta$  4.33 ( $J = 5.2, 11.9$  Hz, 1H) as a doublet of doublets as well as up field shift of H-3 proton at  $\delta$  4.62 as broad singlet (about 1 ppm, as compared with same proton in compound **7**) confirmed the formation of products. This same pattern of protons observed in the  $^1\text{H}$  NMR of compound **8b**. The FABMS of compounds **8a** and **8b** show ( $M^+$ +1) peaks at 273 and 301 respectively further confirmed the product **8a** and **8b**. The optical rotation of syributins 1 (**8a**) and 2 (**8b**)  $[\alpha]_D +6.4$  (c 0.4,  $\text{CHCl}_3$ ) and  $[\alpha]_D +7.4$  (c 0.4,  $\text{CHCl}_3$ ) respectively, were in good accordance with those of the natural products. Pleasingly, the IR, mass and  $^{13}\text{C}$  NMR data of the synthetic syributins were in good accordance with those of the natural product.

In conclusion, the total synthesis of syributins **8a** and **8b** was successfully accomplished in seven steps starting from the Baylis-Hillman adduct of 2,3-*O*-isopropylidene-*R*-glyceraldehyde-ethyl acrylate followed by RCM as the key step.



Scheme 2



Scheme 1

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