Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 4773–4775
Tetrahedron Letters

Use of a Baylis–Hillman adduct in the stereoselective synthesis of syributins via a RCM protocol ☆

Palakodety Radha Krishna,* M. Narsingam and V. Kannan

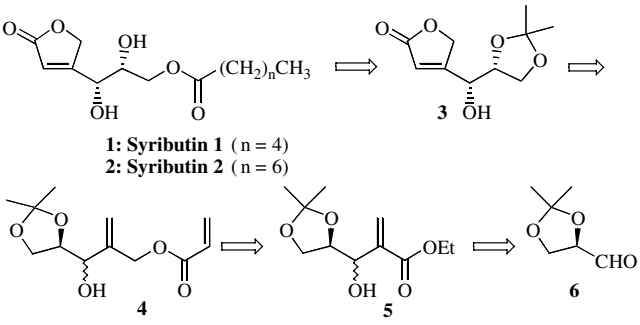
D-206/B, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 25 February 2004; revised 1 April 2004; accepted 8 April 2004

Abstract—The total synthesis of syributins **1** and **2** using the Baylis–Hillman adduct of 2,3-*O*-isopropylidene-*R*-glyceraldehyde-ethyl acrylate as starting material followed by ring closing metathesis (RCM) of the acrylate derivative of the ensuing diol as the key step is reported.

The syributins along with secosyrins were isolated by Sims and co-workers[1] as the co-isolates of syringolide elicitors from *pseudomonas syringea* pv. *tomato* expressing virulence gene D (*avr*D-genes). While syringolides are of interest due to their unusual response to resistant soyabean plants, syributins,[1–4] and secosyrins[1,3,4] gained importance owing to their interesting structural features and their potential properties of providing vital clues to the biosynthesis of syringolides. Although structurally related they do not display the same activity profile as syringolides. Recently, a diastereoselective Baylis–Hillman reaction using sugar-derived aldehydes as the chiral electrophiles was developed in our laboratories.[5] The total synthesis of syributins **1** and **2** was undertaken to exemplify the synthetic utility of one such Baylis–Hillman adduct. Herein we describe the total synthesis of syributins **1** and **2** using the Baylis–Hillman adduct of 2,3-*O*-isopropylidene-*R*-glyceraldehyde-ethyl acrylate as the starting material and RCM of the monoacrylate of the ensuing diol as the key step for the construction of the lactone ring.

Retrosynthetic analysis of **1** and **2** as delineated in Scheme 1 revealed that the lactone **3** is an appropriate intermediate for further manipulation to the target compounds. Lactone **3** in turn could be envisaged from



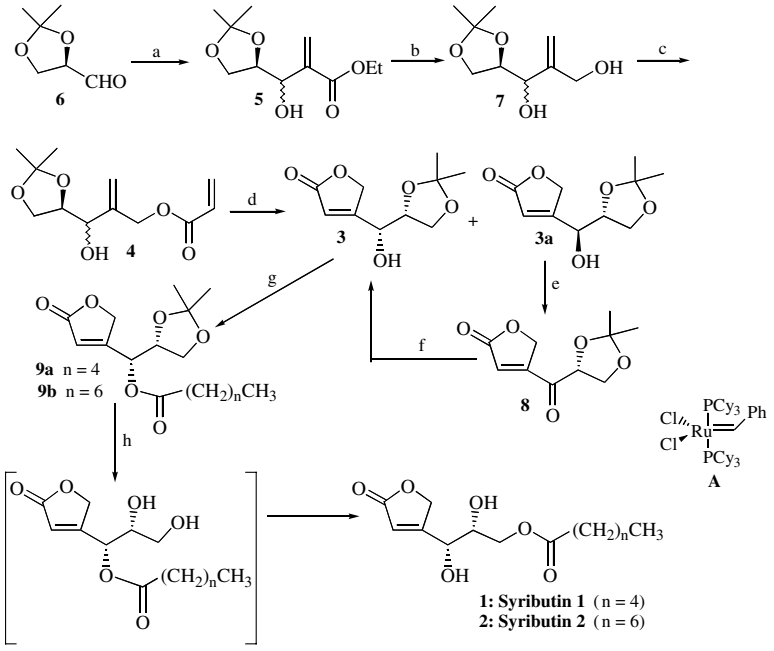
Scheme 1. Retrosynthetics of syributins **1** and **2**.

the monoacrylate **4** by RCM and **4** could be readily accessed from **5**, a Baylis–Hillman adduct obtained by the reaction between 2,3-*O*-isopropylidene-*R*-glyceraldehyde **6** and ethyl acrylate.

Accordingly, the Baylis–Hillman reaction of 2,3-*O*-isopropylidene-*R*-glyceraldehyde **6** with ethyl acrylate was performed in 1,4-dioxane:water[6] as solvent and DABCO as catalyst (Scheme 2). The reaction was complete in 24 h affording **5** (72%). The de of adduct **5** was found to be 80% by ^{1}H NMR and HPLC analysis. Although the Baylis–Hillman reaction of 2,3-*O*-isopropylidene-*R*-glyceraldehyde **6** with ethyl acrylate has been performed[7] at high pressure (4 kbar), no diastereoselectivity was obtained. Thus the use of 1,4-dioxane:water not only facilitates the Baylis–Hillman reaction at normal atmospheric pressure and temperature but also resulted in adduct **5** with 80% de. The absolute stereochemistry of

Keywords: 2,3-*O*-Isopropylidene-*R*-glyceraldehyde; Ethyl acrylate; Baylis–Hillman reaction; Ring-closing metathesis; Syributins.
☆ IICT Communication No. 040202.
* Corresponding author. Fax: +91-40-27160387; e-mail: prkgenius@iict.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.080



Scheme 2. Reagents and conditions: (a) ethyl acrylate, DABCO, 1,4 dioxane, H_2O (1;1), rt, 24 h, 72%; (b) LAH, $AlCl_3$, ether, 0 °C, 2 h, 65%; (c) acryloyl chloride, *N*-ethyldiisopropylamine, CH_2Cl_2, 0 °C to rt, 10 h, **4** (75%), **4a** (10%); (d) Grubbs' catalyst (**A**, 30 mol %), CH_2Cl_2, reflux, 48 h, 62% (**3/3a**, 1:9); (e) PDC, CH_2Cl_2, rt, 12 h, 95%; (f) $LiEt_3BH$, THF, −78 °C, 1.5 h, 100%; (g) **9a**: $CH_3(CH)_4COCl$, Et_3N, CH_2Cl_2, rt, 0.5 h, 87%; **9b**: $CH_3(CH)_6COCl$, Et_3N, CH_2Cl_2, rt, 0.5 h, 90%; (h) TsOH, MeOH, rt, 2 h, **1** (90%); **2** (86%).

the major isomer of **5** was assigned as *S* based on literature[5] evidence. The observed stereoselectivity of **5** can be explained by the favorable attack of the carbanion from the *si*-face of the sugar aldehyde leading to the '*S*' isomer as the major product at the newly created center according to the Felkin–Anh model[8] by a non-chelation protocol.

Adduct **5** was reduced with LAH and $AlCl_3$[9] to afford diol **7**, which on acryloylation (acryloyl chloride, *N*-ethyldiisopropylamine, CH_2Cl_2, rt) afforded monoacylate **4** as the major product (75%) along with diacrylate **4a** (10%). Monoacrylate **4** was subjected to RCM with Grubbs' catalyst[10] (standard ruthenium complex **A**, 30 mol %, CH_2Cl_2, reflux) to afford **3** and **3a** in a moderate yield (62%, 1:9), which were separated by column chromatography. The major isomer **3a** on oxidation with PDC afforded ketone **8**, which on reduction with super-hydride[3] gave the required isomer **3**. Interestingly, lactone **3** is an important advanced intermediate used in the total synthesis of several natural products such as syringolides, spyhydrofurans, and secosyrins.[3] Upon acylation of **3** with hexanoyl chloride and octanoyl chloride, **9a** (87%) and **9b** (90%) were obtained, respectively. Deprotection of the acetonide group (PTSA in methanol) in **9a** and **9b** afforded syributins **1** and **2** via a simultaneous 1,3-acyl migration. Additionally, the total synthesis of syributins **1** and **2** unequivocally confirmed the stereochemistry at the newly created center of the major isomer of **5** as *S*.

In conclusion, the total synthesis of syributins **1** and **2**[11] 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.

Acknowledgements

The authors thank Dr. G. V. M. Sharma for his constant encouragement and keen interest in this work. Two of the authors (M.N. and V.K.) thank CSIR, New Delhi for financial support in the form of fellowships.

References and notes

1. Midland, S. L.; Keen, N. T.; Sims, J. J. *J. Org. Chem.* **1995**, *60*, 1118.
2. Honda, T.; Mizutani, H.; Kanai, K. *J. Org. Chem.* **1996**, *61*, 9374.
3. (a) Yu, P.; Yang, Y.; Zhang, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 6359; (b) Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465.
4. Carda, M.; Castillo, E.; Rodriguez, S.; Falomir, E.; Marco, J. A. *Tetrahedron Lett.* **1998**, *39*, 8895.
5. Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888.
6. Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.
7. Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969.
8. Roush, W. R.; Adam, M.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.
9. Jorgenson, M. J. *Tetrahedron Lett.* **1962**, *13*, 559.
10. Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
11. Spectral data for selected compounds. Compound **5**: HPLC {column: chiralcel OD, 0.5:9.5 ^{i}PrOH/*n*-hexane, flow rate: 1 mL/min, t_r(major) = 22.5 min), t_r(minor) =

23.6 min}; $[\alpha]_D^{25}$ −6.4 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 6.38 (s, 0.1H), 6.36 (s, 0.9H), 5.99 (s, 1H), 4.50 (dd, 1H, $J = 4.5$, 10.4 Hz), 4.38–4.23 (m, 3H), 3.91 (d, 2H, $J = 7.5$ Hz), 2.94 (d, 1H, $J = 4.5$ Hz, OH), 1.45 (s, 3H), 1.38–1.32 (m, 6H); IR (neat) ν 3395, 1750, 1668 cm^{-1}; EIMS: m/z 215 (M^+-15); Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38, H, 7.88; found: C, 57.48, H, 7.87. Compound **3**: $[\alpha]_D^{25}$ −12.7 (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS) δ 5.97 (s, 1H), 4.87 (br. s, 2H), 4.51 (d, $J = 3.7$ Hz, 1H), 4.18 (q, $J = 5.9$ Hz, 1H), 4.06 (dd, $J = 6.6$, 8.0 Hz, 1H), 3.87 (dd, $J = 5.9$, 8.8 Hz, 1H), 2.78 (br. s, 1H, OH), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 173.16, 168.44, 116.70, 116.30, 110.42, 96.12, 69.15, 65.66, 26.38, 24.79; FABMS: m/z 215 (M^++1); Anal. Calcd $C_{10}H_{14}O_5$: C, 56.07, H, 6.59; found: C, 56.02, H, 6.54. **1**: $n = 4$, $[\alpha]_D^{25}$ +6.4 (*c* 0.4, $CHCl_3$); lit.[3a] $[\alpha]_D^{20}$ +6.09 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, TMS) δ 6.07 (s, 1H), 4.94 (ddd, $J = 17.9$, 1.6, 1.1 Hz, 2H), 4.62 (br. s, 1H), 4.33 (dd, $J = 5.2$, 11.9 Hz, 1H), 4.18 (dd, $J = 6.4$, 11.9 Hz, 1H), 3.97–3.93 (m, 1H), 2.36 (t, $J = 7.6$ Hz, 2H), 1.68–1.62 (m, 2H), 1.35–1.28 (m, 4H), 0.9 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ 174.53, 173.33, 169.08, 116.85, 71.60, 68.87, 64.82, 34.07, 31.25, 29.70, 24.53, 22.25, 13.84; FABMS: m/z 273 (M^++1); Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34, H, 7.40; found: C, 57.08, H, 7.39. **2**: $[\alpha]_D^{25}$ +7.4 (*c* 0.4, $CHCl_3$); lit.[3a] $[\alpha]_D^{20}$ +7.03 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 6.03 (s, 1H), 4.90 (ddd, $J = 17.9$, 1.8, 0.6 Hz, 2H), 4.60 (br. s, 1H), 4.21 (dd, $J = 5.2$, 11.7 Hz, 1H), 4.13 (dd, $J = 5.2$, 11.7 Hz, 1H), 3.95–3.89 (m, 1H), 2.30 (t, $J = 6.5$ Hz, 2H), 1.68–1.58 (m, 2H), 1.28–1.19 (m, 8H), 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, TMS) δ 174.98, 173.67, 169.27, 116.64, 72.33, 71.99, 69.37, 64.91, 34.07, 31.59, 29.02, 28.80, 24.83, 22.55, 14.02; FABMS: m/z 301 (M^++1); Anal. Calcd $C_{15}H_{24}O_6$: C, 59.99, H, 8.05; found: C, 59.85, H, 8.02.