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Elaboration of a Baylis–Hillman adduct to (−)-acaterin and its diastereomer through ring closing metathesis

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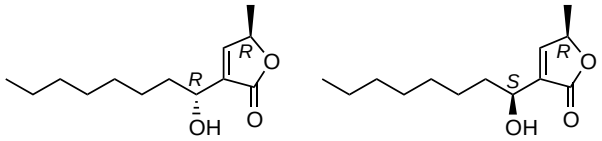
Abstract—A short and efficient synthesis of acaterin, a biologically important natural product has been achieved by elaboration of a Baylis–Hillman adduct. The key step for the synthesis is a ring closing metathesis reaction using Grubbs' catalyst.

The Baylis–Hillman reaction[1,2] has attracted the attention of many synthetic organic chemists because the resulting adducts can be transformed into a variety of natural and unnatural compounds.[3] Several biologically important natural products such as (+)-mikanecic acid,[4] (±)-sarkomycin ester,[5] sitophilate,[6] epopromycin B,[7a] and (−)-mycestericin E[7b] have been synthesized using this reaction as a key step. While working on the asymmetric version of Baylis–Hillman reaction, we discovered that some of its adducts can be used in the synthesis of acaterin (−)-**1** and its diastereomer **2**. Acaterin, isolated from a culture broth of *Pseudomonas* sp. A92 by Endo and co-workers,[8] is an inhibitor of acyl-CoA cholesterol acyltransferase (ACAT). These inhibitors are expected to be effective for treatment of atherosclerosis and hypercholesterolemia. The absolute stereochemistry of natural acaterin (−)-**1** was confirmed after the synthesis of all the diastereomers of acaterin by Kitahara and co-workers.[9,10] The ACAT inhibition activity of all four possible stereoisomers of acaterin was tested using microsomes prepared from rat liver and it was found that all the diastereomers including the natural one showed a similar activity. We disclose here a short and efficient synthesis of natural acaterin **1** and its diastereomer **2** from a Baylis–Hillman adduct through ring closing metathesis (RCM).

Our strategy towards the synthesis of (−)-acaterin **1** and its diastereomer **2** is presented in Scheme 1. The Baylis–Hillman reaction of caprylic aldehyde with methyl acrylate in the presence of a catalytic amount of quinuclidine[11] gave an adduct **3** in 72% isolated yield.[12] We planned to protect the hydroxyl group of **3** and then hydrolyze the ester. It was observed that the hydrolysis of the TBDMS ether protected ester gave poor yields (30%) of the acid even under mild conditions (1N LiOH in THF:H_2O). All attempts to improve the yield of the acid using other reagents and conditions failed. However, a very clean hydrolysis was obtained when the hydroxyl group of **3** was protected as its methoxyethoxymethyl (MEM) ether. Thus, when **4** was treated with 1N LiOH solution in a mixture of THF and water at rt, the desired acid **5** was obtained in a quantitative yield. The acid **5** was coupled with *R*-(−)-3-buten-2-ol in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) to provide **6** as an inseparable mixture of diastereomers, a substrate for RCM. Although electron deficient olefins in general and acrylates, in particular, are known to be problematic substrates for RCM, some successful reports are known using Grubbs catalyst.[13] It was heartening to discover that treatment of **6** with Grubbs' catalyst in DCM under dilute conditions[14] gave a 1:1 diastereomeric mixture of cyclized products **7**[15] and **8**,[16] which were separated by radial chromatography and their absolute configurations were assigned after conversion to natural acaterin **1**[17] and its diastereomer **2**[18] using $TiCl_4$.



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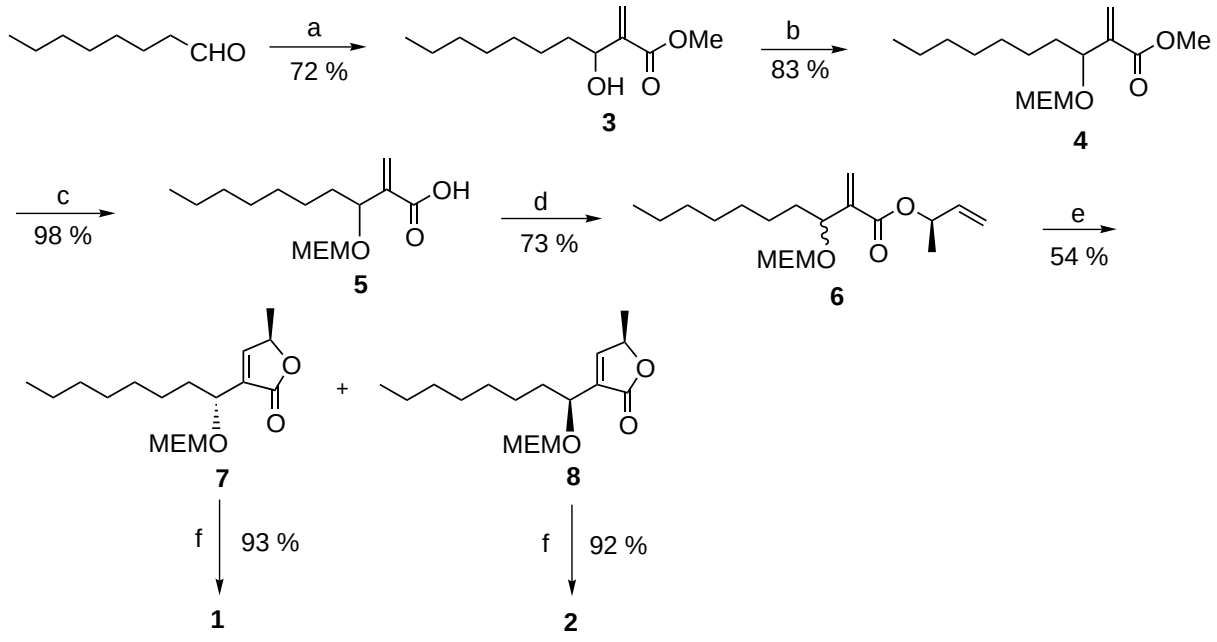

Scheme 1. (a) Methyl acrylate, quinuclidine, 48 h; (b) 2-methoxyethoxymethyl chloride, *N*-ethyl diisopropylamine, DCM, 6 h. (c) 1N aq. LiOH, THF/water (2:1), 24 h; (d) *R*-(−)-3-buten-2-ol, DCC, DMAP, DCM, 24 h; (e) Grubbs' catalyst (30 mol%), DCM, reflux, 48 h; (f) $TiCl_4$, DCM, 8 h.

In conclusion, we have accomplished a short synthesis of natural (−)-acaterin **1** and its diastereomer **2** in an overall yield of 22%.

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14. **6** was cyclized as follows: A solution of Grubbs' catalyst (358 mg, 0.44 mmol) in dry DCM (100 mL) was added dropwise to a stirred solution of the diene **6** (500 mg, 1.45 mmol) in dry DCM (100 mL) at 40°C over a period of 1.5 h. The resulting solution was allowed to stir at reflux for 48 h. The solvent was distilled under reduced pressure and the residue was passed through a short plug of silica gel to give a 1:1 diastereomeric mixture of products (**7** and **8**) as a pale brown liquid (246 mg, 54%). These diastereoisomers were easily separated by radial chromatography using 1–2 mm thick plates coated with silica gel PF_{254} (E-Merck) to give **7** (116 mg) and **8** (110 mg).

15. **7** was characterized as: R_f 0.48 (50% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ +21.9 (*c* 0.60, $CHCl_3$); IR (film) 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, $J=6.4$ Hz, 3H), 1.26–1.29 (m, 10H), 1.43 (d, $J=6.8$ Hz, 3H), 1.71–1.78 (m, 2H), 3.38 (s, 3H), 3.54 (t, $J=4.9$ Hz, 2H), 3.64–3.69 (m, 1H), 3.73–3.78 (m, 1H), 4.48 (t, $J=6.1$ Hz, 1H), 4.73 (d, $J=2.4$ Hz, 2H), 5.04 (q, $J=6.8$ Hz, 1H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.07, 19.08, 22.61, 25.05, 29.18, 29.32, 31.77, 33.89, 59.06, 67.37, 71.54, 71.66, 77.58, 94.10, 134.88, 150.71, 171.84. Mass (EI, *m*/*z*): 269 (base peak). Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.97; H, 9.95. Found: C, 64.84; H, 9.97.
16. **8** was characterized as: R_f 0.5 (50% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ −82.4 (*c* 0.85, $CHCl_3$); IR (film) 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, $J=6.6$ Hz, 3H), 1.26–1.29 (m, 10H), 1.43 (d, $J=6.8$ Hz, 3H), 1.72–1.80 (m, 2H), 3.39 (s, 3H), 3.54 (t, $J=4.9$ Hz, 2H), 3.64–3.69 (m, 1H), 3.74–3.79 (m, 1H), 4.48 (t, $J=6.3$ Hz, 1H), 4.73 (s, 2H), 5.05 (q, $J=6.8$ Hz, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.06, 19.11, 22.60, 25.13, 29.18, 29.32, 31.78, 33.92, 59.05, 67.36, 71.55, 71.66, 77.58, 94.12, 134.85, 150.67, 171.86. Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.97; H, 9.95. Found: C, 64.94; H, 9.92.
17. The spectral data of the natural acaterin (−)-**1** was identical with that reported.[9] It was characterized as: R_f 0.40 (50% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ −18.9 (*c* 0.95, $CHCl_3$) {lit.[8] $[\alpha]_D^{19}$ −17 ($CHCl_3$); lit.[9] $[\alpha]_D^{20}$ −19.7 (*c* 0.61, $CHCl_3$)}; IR (film) 3458, 1750, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J=7.1$ Hz, 3H), 1.27–1.30 (m, 10H), 1.45 (d, $J=6.8$ Hz, 3H), 1.64–1.81 (m, 2H), 2.69 (bs, 1H), 4.47–4.50 (m, 1H), 5.07 (q, $J=6.8$ Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 18.90, 22.59, 25.23, 29.15, 29.28, 31.73, 35.41, 66.99, 77.95, 136.15, 149.32, 172.67.
18. The pseudo acaterin **2** was characterized as: R_f 0.42 (50% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ −54.7 (*c* 0.75 in $CHCl_3$) {lit.[9] $[\alpha]_D^{25}$ −63.7 (*c* 0.53, $CHCl_3$)}; IR (film) 3458, 1750, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J=7.1$ Hz, 3H), 1.27–1.32 (m, 10H), 1.44 (d, $J=6.8$ Hz, 3H), 1.66–1.81 (m, 2H), 2.62 (bs, 1H), 4.49 (m, 1H), 5.07 (q, $J=6.8$ Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 18.93, 22.59, 25.28, 29.16, 29.28, 31.74, 35.43, 67.08, 77.95, 136.21, 149.28, 172.63.