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First stereoselective total synthesis of trichodermone A

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ABSTRACT

The first stereoselective total synthesis of trichodermone A using Baylis–Hillman and ring-closing metathesis (RCM) reactions as key steps is reported.

The genus *Trichoderma* is well known for its bio-control constituents and has been extensively investigated.[1] Trichodermone A (**1**) is a new type of cyclopentenone isolated from the strain *Trichoderma* sp. YLF-3 with antibacterial properties.[2] Trichodermone A attracted our attention as the synthetic target primarily due to its fascinating structural features consisting of a highly substituted cylcopentenone system with two stereogenic centers; one on the ring skeleton and the other one as an appendage at C3 in the form of a '1′*S*-hydroxy ethyl' moiety. The labile hydroxyl functionality at C4 and a base-sensitive C5-methylene next to the ketone functionality add up to the synthetic difficulty. Herein we report the first stereoselective total synthesis of trichodermone A (**1**) from the commercially available starting material acetaldehyde (**6**) by adopting the synthetic route as depicted in Scheme 1.

For the last few years we have been involved in expanding the horizon of asymmetric Baylis–Hillman reaction[3a] and found varied applications of the corresponding adducts.[3b–d] Furthering their use in natural product chemistry[3b] we identified the optically pure adduct **5** (Scheme 1) that could be realized from the Baylis–Hillman reaction between acetaldehyde (**6**) and ethyl acrylate followed by the Sharpless kinetic resolution as an ideal starting material for the synthesis of **1**. The second stereogenic center was planned through the Sharpless asymmetric epoxidation of the allyl alcohol derived from **5** (vide infra Scheme 2) and the reductive ring-opening reaction of the corresponding epoxide to afford the 1,3-diol **4**. Diol **4** on chain extension first leads to the bis-olefin **3** which on Hoveyda–Grubbs catalyst-assisted RCM results in the cyclopentenol **2** that could be conveniently elaborated to the target compound **1**.

Thus, the synthesis (Scheme 2) of **1** starts from the known[4] acetaldehyde Baylis–Hillman adduct **7**, which on Sharpless kinetic resolution[5] {(−)-DIPT/Ti(O^iPr)$_4$/CHP/CH_2Cl_2/−20 °C/45%} gave the desired chiral BH-adduct **5** as an optically pure *S*-isomer.[4] Hydroxy functionality in adduct **5** was protected as its MOM-ether **8** (MOMCl/DIPEA/CH_2Cl_2/rt/99%) and the ester functionality was reduced (DIBAL-H/CH_2Cl_2/0 °C/3 h/89%) to its corresponding alcohol **9**. Primary alcohol on Swern oxidation followed by Wittig olefination reaction afforded the conjugated ester **10** (96% over two steps), which on reduction with DIBAL-H gave the allylic alcohol **11**. Allylic alcohol **11** was converted to epoxy alcohol **12** using Sharpless epoxidation[6] conditions {(+)-DIPT/Ti(O^iPr)$_4$/CHP/CH_2Cl_2/−20 °C/92%}. Reductive ring-opening reaction of **12** with Red-Al in CH_2Cl_2 afforded the desired 1,3-diol **4** in good yield. Primary alcohol of diol **4** was protected as its benzoate ester (Bz-Cl/Et_3N/DMAP/rt/2 h/89%) and the secondary alcohol as its MOM-ether (MOMCl/DIPEA/CH_2Cl_2/rt/99%) to furnish the all protected intermediate **13**. Deprotection (K_2CO_3/MeOH/rt/1 h/87%) of benzoyl group gave the primary alcohol **14**.

Next, the homologation of compound **14** to the RCM precursor **3** was planned in the following way. Firstly, the alcohol **14** was oxidized under Swern conditions to afford the corresponding aldehyde which was subjected to vinylation reaction (vinylMgBr/THF/−20 °C/20 min/83%) without any purification to afford the bis-olefin **3** as a 1:1 diastereomeric mixture. No efforts were made to separate the isomers because the carbon bearing the newly generated hydroxyl group later transforms into a ketone functionality.

Subsequently, the bis-olefin **3** on Hoveyda–Grubbs catalyst[7] (10 mol %) assisted ring-closing metathesis (RCM) under refluxing conditions in toluene gave the MOM-protected cyclopentenol **2**

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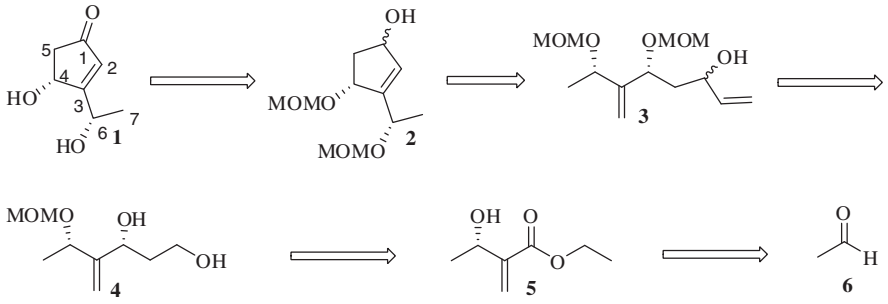
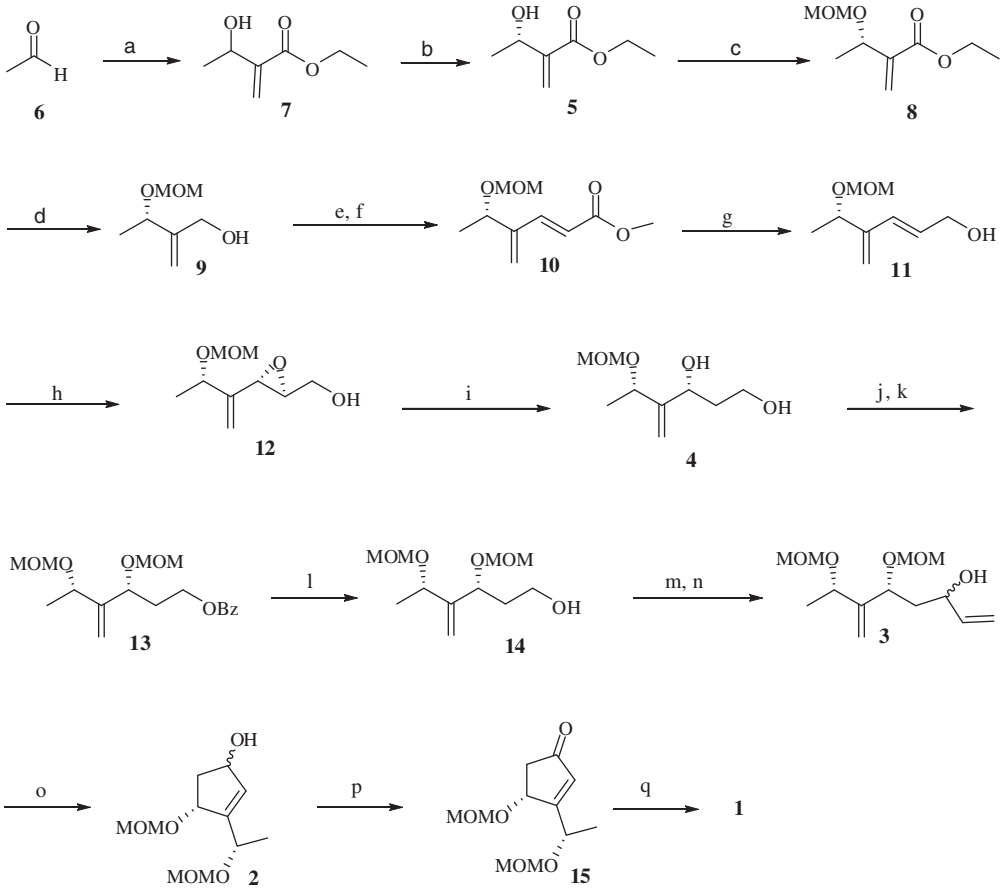


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) ethyl acrylate, DABCO, DMF 12 h, 85%. (b) (−)-DIPT, $Ti(O^iPr)_4$, CHP, −20 °C, 4d, 45%. (c) MOM-Cl, DIPEA, CH_2Cl_2, 12 h, 99%. (d) DIBAL-H, CH_2Cl_2, 0 °C, 3 h, 89%. (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, 98%. (f) PPh_3=COOMe, CH_2Cl_2, 0 °C, 3 h, 98%. (g) DIBAL-H, CH_2Cl_2, 0 °C, 3 h, 86%. (h) (+)-DIPT, $Ti(O^iPr)_4$, CHP, −20 °C, 12 h, 92%. (i) Red-Al CH_2Cl_2, 0 °C, 3 h, 79%. (j) Bz-Cl, Et_3N, DMAP, 2 h, 89%. (k) MOM-Cl, DIPEA, CH_2Cl_2, 12 h, 99%. (l) K_2CO_3, MeOH, 1 h, 87%. (m) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, 98%. (n) VinylMgBr, THF, −20 °C, 20 min, 83%. (o) HG-2nd generation catalyst (10 mol %), toluene, reflux, 5 h, 94%. (p) DMP, CH_2Cl_2, 0 °C. (q) TFA, CH_2Cl_2, 0 °C, 2 h, 98%.

(94%) as an inseparable 1:1 diastereomeric mixture. ^{1}H NMR spectrum of compound **2** revealed the lone olefinic proton resonating at δ 5.89 ppm as a doublet (J = 11.7 Hz). The HRMS spectrum displayed the $[M+Na]^+$ 255.1465, calculated 255.1463 for the molecular formula $C_{11}H_{20}O_5Na$. Cyclopentenol **2** on oxidation[8] (Dess–Martin periodinane/CH_2Cl_2/0 °C/93%) gave cyclopentenone **15**. Finally, deprotection of the MOM groups in **15** with TFA gave the trichodermone A **1**. Compound **1** was characterized by its spectral data and was found consistent with the reported values.[2,9] Thus the ^{1}H NMR spectrum of **1** revealed the lone olefinic proton resonating at δ 6.09 ppm as a singlet and one of the allylic protons (H-4) resonating at δ 5.07 ppm as a broad doublet (J = 5.3 Hz) while the other one (H-6) resonated at δ 4.93 ppm as a quartet (J = 6.4 Hz). The protons due to C5-methylene group displayed an AB multiplicity pattern with one of the diastereotopic protons appearing at δ 2.86 ppm as a doublet of doublet (J = 6.4, 18.5 Hz) and the other one resonated at δ 2.42 ppm also as a doublet of doublet (J = 1.8, 16.7 Hz). The protons due to the methyl group appeared at δ 1.53 ppm as a doublet (J = 6.7 Hz). The HRMS spectrum displayed $[M+Na]^+$ 165.1269, calculated 165.1266 for the molecular formula $C_7H_{10}O_3Na$.

In summary, we described the first stereoselective total synthesis of trichodermone A using Baylis–Hillman reaction and RCM as the key steps.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.081.

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9. *Spectral data for selected compounds*: *Compound* **5**: colorless syrup. $[\alpha]_D^{25}$ −18.0 (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.17 (s, 1H), 5.78 (s, 1H), 4.57 (q, 1H, *J* = 6.4, 12.8 Hz), 4.20 (q, 2H, *J* = 6.9, 7.1 Hz), 1.38–1.31 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 143.4, 123.9, 67.6, 61.2, 21.9, 14.1. ESIMS: *m*/*z* 167 $(M+Na)^+$. IR (neat): 3448, 1622, 1747 cm^{-1}. *Compound* **12**: colorless syrup. $[\alpha]_D^{25}$ −84.0 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (d, 2H, *J* = 10.1 Hz), 4.54 (d, 1H, *J* = 6.7 Hz), 4.51 (d, 1H, *J* = 6.7 Hz), 4.21 (q, 1H, *J* = 6.6, 13.2 Hz), 3.84 (d, 1H, *J* = 11.2 Hz), 3.68 (d, 1H, *J* = 13.5 Hz), 3.39 (d, 1H, *J* = 1.9 Hz), 3.38 (s, 3H), 2.95–2.92 (m, 1H), 1.34 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.3, 111.7, 94.7, 73.0, 61.8, 61.0, 56.1, 54.7, 21.6. ESIMS: *m*/*z* 211 $(M+Na)^+$. IR (neat): 3450, 1629 cm^{-1}. *Compound* **3**: colorless syrup. $[\alpha]_D^{25}$ +114.0 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.91–5.77 (m, 1H), 5.25 (d, 1H, *J* = 10.5 Hz), 5.23 (s, 2H), 5.09 (d, 1H, *J* = 10.5 Hz), 4.61–4.35 (m, 6H), 4.20 (q, 1H, *J* = 6.6, 12.8 Hz), 3.39 (s, 3H), 3.33 (s, 3H), 1.81–1.75 (m, 2H), 1.29 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 140.4, 114.2, 96.0, 93.9, 93.4, 75.2, 72.2, 71.6, 55.8, 55.2, 42.8, 20.6. IR (neat): 3345, 1625 cm^{-1}. ESIMS: *m*/*z* 283 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{13}H_{24}O_5Na$: 283.1322. Found: 283.1328. *Compound* **2**: colorless syrup. $[\alpha]_D^{25}$ −46.5 (*c* 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.89 (d, 1H, *J* = 11.7 Hz), 4.73–4.62 (m, 6H), 4.49–4.42 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 1.76–1.67 (m, 2H), 1.31 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.2, 131.5, 94.6, 95.5, 79.1, 73.9, 69.5, 55.8, 42.2, 21.0. IR (neat): 3552, 1632 cm^{-1}. ESIMS: *m*/*z* 255 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{11}H_{20}O_5Na$: 255.1463. Found: 255.1465. *Compound* **15**: colorless syrup. $[\alpha]_D^{25}$ −133.1 (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.21 (s, 1H), 4.82 (br d, 1H, *J* = 6.0 Hz), 4.75–4.64 (m, 5H), 3.42 (s, 3H), 3.40 (s, 3H), 2.77 (dd, 1H, *J* = 6.0, 12.0 Hz), 2.41 (dd, 1H, *J* = 2.2, 15.5 Hz), 1.41 (3H, d, *J* = 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4, 179.5, 129.8, 96.3, 94.9, 74.1, 69.6, 56.0, 55.4, 43.3, 19.6. IR (neat): 1735, 1620 cm^{-1}. ESIMS: *m*/*z* 253 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_{11}H_{18}O_5Na$: 253.1139. Found: 253.1134. *Compound* **1**: solid. Mp 99–101. $[\alpha]_D^{25}$ −27.5 (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.09 (s, 1H, H-2), 5.07 (br d, 1H, *J* = 5.3 Hz, H-4), 4.93 (q, 1H, *J* = 6.4 Hz, H-6), 2.86 (dd, 1H, *J* = 6.4, 18.5 Hz, H-5), 2.42 (dd, 1H, *J* = 1.8, 16.7, Hz, H-5), 1.53 (d, 3H, *J* = 6.7 Hz, H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 181.5, 129.0, 71.2, 67.0, 45.3, 22.5. IR (neat): 3435, 1742, 1621 cm^{-1}. ESIMS: *m*/*z* 165 $(M+Na)^+$, HRMS *m*/*z*: Calcd for $C_7H_{10}O_3Na$: 165.1266. Found: 165.1269.