Application of a Stereoselective Rhodium(II)-Catalyzed Oxonium Ylide Formation–[2,3]-Sigmatropic Rearrangement of an α-Diazo-β-keto Ester to the Synthesis of 2-*epi*-Cinatrin C_1 Dimethyl Ester

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Abstract: The $Rh_2(OAc)_4$-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of a highly functionalized α-diazo-β-keto ester derived from D-glucose proceeded stereoselectively to give the corresponding tetrahydrofuran-3-one as a single diastereomer in high yield. This reaction was applied to the synthesis of 2-*epi*-cinatrin C_1 dimethyl ester as a key step.

Key words: diazoketo ester, rhodium(II) catalyst, oxonium ylide, [2,3]-sigmatropic rearrangement, cinatrin

Metal carbenes derived from α-diazocarbonyl compounds are highly electrophilic and react with an available Lewis base to form an ylide. When the resulting ylide has an allylic substituent at the proper position, a subsequent [2,3]-sigmatropic rearrangement takes place. Such metal-catalyzed carbenoid reactions have become a powerful tool for the synthesis of functionalized cyclic compounds including oxacycles.[1] We recently reported a stereoselective copper-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement reaction of an α-diazo ketone to give 2,6-*trans*-dihydropyran-3-one[2] and a rhodium(II)-catalyzed reaction of α-diazo-β-keto esters leading to 3-oxotetrahydrofurans.[3]

A family of cinatrins, which were isolated from the fermentation broth of the microorganism *Circinotrichum falcatisporum* RF-641 by Itazaki and co-workers, possess phospholipase A_2 inhibitory activity.[4] Among them, the cinatrins A and B have a unique spirolactone skeleton as a key structural component, whereas cinatrin C_1 (**1**) contains a highly substituted γ-lactone framework that appears to be a ring-opened derivative of cinatrin B (Figure 1). The stereoselective construction of substituted γ-lactones with three continuous stereocenters is one of the most important issues for the synthesis of these attractive bioactive compounds.[5]

Here we report the stereoselective rhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement of α-diazo-β-keto ester **4** derived from D-glucose and its application to the synthesis of 2-*epi*-cinatrin C_1 dimethyl ester **2**.

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The outline of our synthesis of cinatrins is illustrated in Scheme 1. Cinatrins are generated from a key intermediate, a substituted tetrahydrofuran-3-one **3**, by (a) oxidation to a lactone, (b) introduction of the C1 unit, and (c) extension of the side chain. Furanone **3** is stereoselectively synthesized from α-diazo-β-keto ester **4** by using the rhodium(II)-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement. The diazoketo ester **4** is easily prepared from D-glucose.

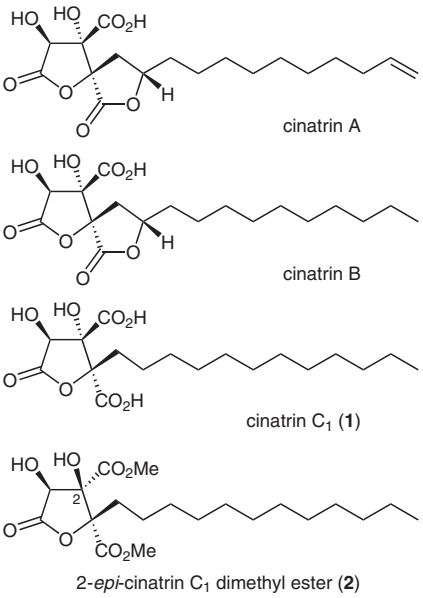
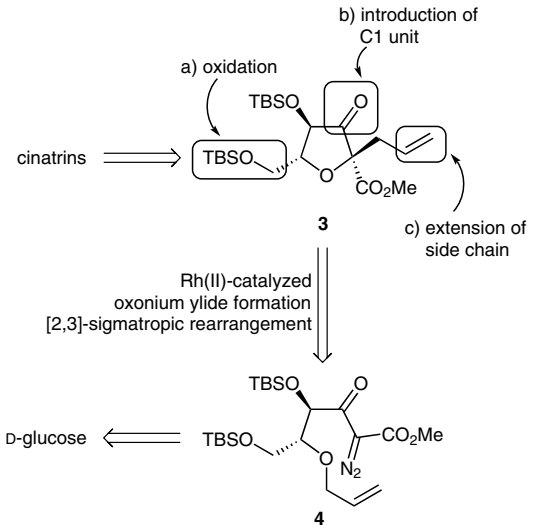
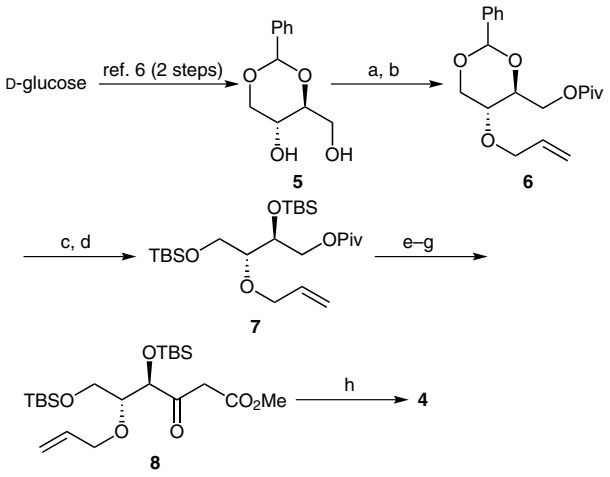


Figure 1 Cinatrin family

We started our synthesis from D-glucose (Scheme 2). According to the reported procedure,[6] diol **5** was prepared from D-glucose in two steps. The selective protection of the primary alcohol by a pivaloyl (Piv) group followed by allylation of the remaining secondary alcohol gave **6**. The benzylidene diol protecting group was changed to a *tert*-butyldimethylsilyl (TBS) group, leading to bis-TBS ether **7**. The removal of the Piv group by diisobutylaluminum hydride (DIBAL-H) reduction, oxidation to the aldehyde, and subsequent β-keto ester formation with methyl diazoacetate in the presence of tin(II) chloride gave keto ester **8**. Subsequently, a diazo transfer reaction converted **8** to α-diazo-β-keto ester **4**.

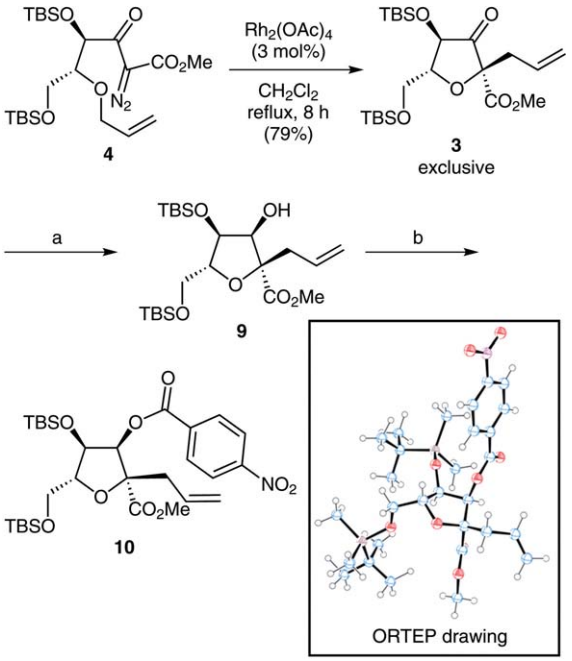


Scheme 1 Retrosynthetic analysis of cinatrins

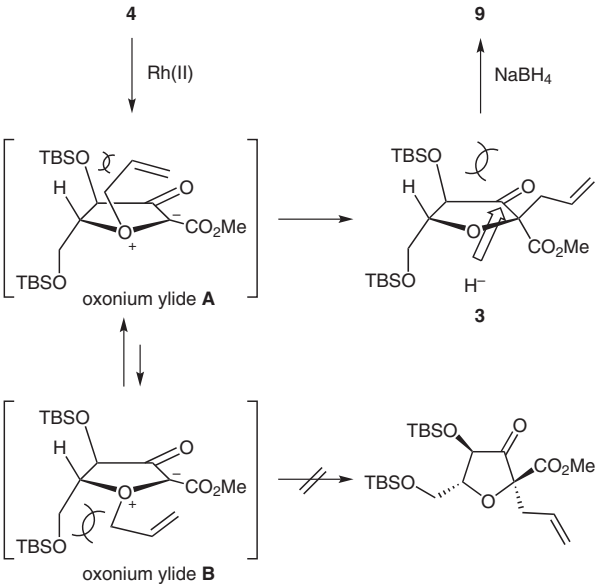


Scheme 2 *Reagents and conditions*: (a) *t*-BuCOCl, pyridine, DMAP, CH_2Cl_2, r.t., 1.5 h, 97%; (b) allyl bromide, Ag_2O, $CaSO_4$, benzene, r.t., 39 h, 90%; (c) CSA, MeOH, r.t., 18.5 h, 89%; (d) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 20 min, 99%; (e) DIBAL-H, CH_2Cl_2, –80 °C, 30 min, 89%; (f) Dess–Martin periodinane, CH_2Cl_2, r.t., 1.5 h, 92%; (g) N_2CHCO_2Me, $SnCl_2$, CH_2Cl_2, r.t., 5.5 h, 75%; (h) TsN_3, Et_3N, MeCN, r.t., 4 h, 96%.

Next, we examined the rhodium(II)-catalyzed reaction of **4**, a key step of our cinatrin synthetic plan (Scheme 3). We recently reported that the rhodium(II)-catalyzed reaction of 5-allyloxy-2-diazo-3-ketoesters gave methyl 5-substituted 2-allyl-3-oxotetrahydrofuran-2-carboxylates in high yields with excellent stereoselectivities.[3] According to the reported procedure,[3] **4** was treated with 3 mol% of dirhodium(II) tetraacetate [$Rh_2(OAc)_4$] in dichloromethane under reflux for eight hours. The reaction smoothly proceeded to give tetrahydrofuran-3-one **3** as a single diastereomer in 79% yield.[7] The reduction of **3** with sodium borohydride produced alcohol **9**, which was esterified with 4-nitrobenzoyl chloride to give a crystalline product, ester **10**.[8] The X-ray analysis of **10** confirmed the *trans* relationship between the 5-silyloxymethyl and 2-allyl groups and showed the 3,4-*cis* stereochemistry. This indicated that the rhodium(II)-catalyzed reaction proceeds via oxonium ylide **A**, which is apparently a more stable intermediate than **B**, and that the subsequent [2,3]-sigmatropic rearrangement of the allyl group from oxygen to carbon formed **3**, consistent with our previously reported stereoselectivity for the reaction of 5-allyloxy-2-diazo-3-ketoesters (Scheme 4). In the subsequent reduction, the hydride should attack the carbonyl group from the α-side to avoid the adjacent bulky α-TBDMSO group of ketone to give β-hydroxy compound **9**.

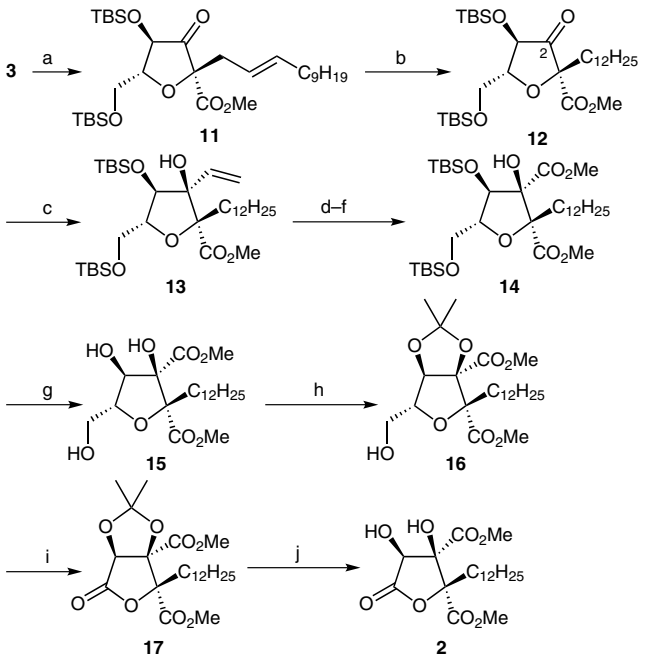


Scheme 3 *Reagents and conditions*: (a) $NaBH_4$, CH_2Cl_2–MeOH, –80 °C, 10 min, 92%; (b) 4-nitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, r.t., 1.5 h, 88%.



Scheme 4 Stereochemical preferences for rhodium(II)-catalyzed reaction of **4** and the following reduction

The excellent stereoselectivity of the $NaBH_4$ reduction of **3** encouraged us to synthesize 2-*epi*-cinatrin C_1 in order to prove the utility of our strategy for the synthesis of cinatrin derivatives (Scheme 5). The chain extension of the allyl group using olefin metathesis with Grubbs' second generation catalyst and 1-undecene gave (*E*)-alkene **11**[9] that was reduced to an alkyl group to give **12** in 91% yield in two steps. The nucleophilic addition of a vinyl group to **12** by using vinylmagnesium bromide exclusively produced α-vinyl adduct **13**. This addition displayed the same stereoselectivity as that observed in the reduction of **3**. The stereochemistry of **13** was confirmed by the subsequent formation of the acetonide of **15**. The vinyl group was next converted to a methoxycarbonyl moiety by the usual three-step protocol to afford **14**. The removal of the two silyl groups gave triol **15**, and the subsequent formation of the acetonide of the *cis*-diol produced **16**. Oxidation of **16** to lactone **17** was achieved by Taber's procedure,[10] whereby the treatment of **16** with pyridinium dichromate (PDC) and acetic anhydride in CH_2Cl_2–*N*,*N*-dimethylformamide (DMF) under reflux resulted in **17**. The final deprotection of the acetonide to diol was troublesome because the typical acidic conditions were not suitable for this transformation. However, the deprotection was achieved by the treatment of **17** with iodine in methanol[11] under reflux to give 2-*epi*-cinatrin C_1 dimethyl ester **2**[12,13] in 84% yield.



Scheme 5 *Reagents and conditions*: (a) 1-undecene, Grubbs' second-generation catalyst, CH_2Cl_2, reflux, 1 h, 96%; (b) 3 atm H_2, Pd/C, EtOH, r.t., 3 h, 95%; (c) vinylmagnesium bromide, THF, –80 °C, 20 min, 85%; (d) O_3, Me_2S, CH_2Cl_2–MeOH, –78 °C, 10 min; (e) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, *t*-BuOH–2-methylbut-2-ene–H_2O, r.t., 1 h; (f) excess CH_2N_2, Et_2O, r.t., 15 min, 82% for 3 steps; (g) concd HCl, MeOH, r.t., 1.5 h, 92%; (h) 2,2-dimethoxypropane, TsOH, 60 °C, 1.5 h, 91%; (i) PDC, Ac_2O, CH_2Cl_2–DMF, reflux, 1.5 h, 71%; (j) I_2, MeOH, reflux, 45 h, 84%.

In conclusion, the $Rh_2(OAc)_4$-catalyzed oxonium ylide formation–[2,3]-sigmatropic rearrangement reaction of α-diazo-β-keto ester **4** derived from D-glucose stereoselectively proceeded to give tetrahydrofuran-3-one **3** as a single diastereomer in high yield. The resulting **3** was converted into 2-*epi*-cinatrin C_1 dimethyl ester **2**. As our results have demonstrated the utility of our strategy for the construction of the core structure of cinatrin derivatives, the stereoselective introduction of the C1 unit at the 2-positon from the β-side and the total synthesis of cinatrin C_1 and its derivatives are now in progress.

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(7) **Rhodium(II)-Catalyzed Reaction of α-Diazo-β-keto Ester 4**: To a solution of $Rh_2(OAc)_4$ (17 mg, 0.038 mmol) in CH_2Cl_2 (40 mL) was added a solution of **4** (618 mg, 1.27 mmol) in CH_2Cl_2 (24 mL). The resulting solution was refluxed for 8 h. After concentration of the reaction, the residue was purified by column chromatography on SiO_2 (5% EtOAc in hexane) to give **3** (459 mg, 79%) as a colorless oil; $[\alpha]_D^{26}$ +12.9 (*c* = 0.750, $CHCl_3$). IR (neat): 1781, 1753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.11 (s, 3 H), 0.18 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 2.61–2.81 (m, 2 H), 3.72 (s, 3 H), 3.82 (dd, *J* = 11.8, 3.0 Hz, 1 H), 3.91 (ddd, *J* = 8.9, 3.0, 2.1 Hz, 1 H), 4.00 (dd, *J* = 11.8, 2.1 Hz, 1 H), 4.57 (d, *J* = 8.8 Hz, 1 H), 5.11–5.21 (m, 2 H), 5.67–5.81 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5, –5.4, –5.3, –4.4, 18.2, 18.3, 25.6 (3), 25.8 (3), 38.4, 52.8, 61.3, 72.3, 80.2, 84.8, 120.2, 130.7, 167.6, 208.6. MS: *m/z* = 459 [M^+ + H]. HRMS (EI): *m/z* calcd for $C_{22}H_{43}O_6Si_2$: 459.2598; found: 459.2578.

(8) Spectroscopic data for **10**: colorless crystals; mp 86–88 °C (from 5% EtOAc in hexane); $[\alpha]_D^{21}$ −30.8° (*c* = 0.5, $CHCl_3$). IR (neat): 1740, 1531 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = −0.04 (s, 3 H), 0.06 (s, 3 H), 0.09 (s, 3 H), 0.10 (s, 3 H), 0.74 (s, 9 H), 0.91 (s, 9 H), 2.74 (dd, *J* = 14.0, 7.4 Hz, 1 H), 2.89 (dd, *J* = 13.6, 7.4 Hz, 1 H), 3.70 (dd, *J* = 11.8, 4.0 Hz, 1 H), 3.73 (s, 3 H), 3.81 (dd, *J* = 11.3, 3.3 Hz, 1 H), 4.08 (dt, *J* = 5.2, 3.3 Hz, 1 H), 4.52 (t, *J* = 4.9 Hz, 1 H), 5.01–5.06 (m, 1 H), 5.08 (br s, 1 H), 5.64–5.79 (m, 1 H), 5.75 (d, *J* = 4.9 Hz, 1 H), 8.25 (d, *J* = 8.8 Hz, 2 H), 8.32 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.53, −5.46, −5.1, −5.0, 17.7, 18.4, 25.5 (3), 25.9 (3), 38.4, 52.4, 62.4, 71.4, 84.9, 86.2, 119.0, 123.7, 130.8, 131.6, 135.2, 160.7, 163.5, 171.7.

MS: *m*/*z* = 610 [M^+ + H]. HRMS (EI): *m*/*z* calcd for $C_{29}H_{48}O_9NSi_2$: 610.2867; found: 610.2868. The X-ray data are now being deposited with the CCDC. CCDC-908929 (for **10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) The coupling constant between the olefinic protons of **11** was observed to be 15.4 Hz.

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(12) Spectroscopic data for **2**: a colorless oil; $[\alpha]_D^{18}$ −35.1° (*c* = 0.750, $CHCl_3$). IR (neat): 3462, 1806, 1748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.25 (br s, 20 H), 1.92 (ddd, *J* = 14.0, 11.8, 4.4 Hz, 1 H), 2.08 (ddd, *J* = 14.0, 11.8, 4.4 Hz, 1 H), 2.93 (d, *J* = 9.1 Hz, 1 H), 3.79 (s, 3 H), 3.86 (s, 3 H), 3.89 (br s, 1 H), 4.99 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 23.2, 29.3, 29.4, 29.56, 29.60, 30.7, 31.9, 53.3, 54.0, 71.3, 81.3, 89.2, 168.9, 169.1, 172.7. MS: *m*/*z* = 402 [M^+]. HRMS (EI): *m*/*z* calcd for $C_{20}H_{34}O_8$: 402.2254; found: 402.2234.

(13) Unfortunately, the treatment of **2** with aqueous sodium hydroxide according to Rizzacasa's cinatrin syntheses (see refs. 5a and 5b) gave a complex mixture. It is very interesting that the stereochemistry of the C-2 position strongly influenced its chemical stability.

