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Unprecedented chemo-enzymatic synthesis of stereochemically pure 3-acetoxy-2-methyl-2-vinylcycloalkanones

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Abstract—A new approach to 3-acetoxy-2-methyl-2-vinylcyclohexanone and 3-acetoxy-2-methyl-2-vinylcyclopentanone in stereochemically pure state, by means of a combination of yeast-catalyzed reduction and subsequent radical β-fragmentation is described.

2,2-Disubstituted-3-hydroxycycloalkanones, which are prepared by baker's yeast-catalyzed reduction of the corresponding diketones, are good starting materials for the construction of a characteristic structural feature with chiral centers (**A**, such as stypoldione, Fig. 1) in natural product synthesis, involving terpenoids, degraded carotenoids, steroids, and related substances, in enantiomerically pure form.[1] For example, Mori has demonstrated a large number of applications on 2,2-dimethyl-3-hydroxycyclohexanone **2a** from 2,2-dimethylcyclohexane-1,3-dione **1a** (Scheme 1).[2]

A problem in this approach is that the range of substrates available to yeast-catalyzed reduction, however, is rather limited. Needless to say, some advanced compounds bearing substituents convertible to oxygen-containing functional groups at the C-2 position (**B**) deserve attention in natural product synthesis such as triptocallol (Fig. 1). Recently, Nakada and co-workers reported an elegant approach,[3] the preparation of 2-benzyloxymethyl-2-methylcyclohexane-1,3-dione **1b**, based on the Birch reduction of 2,6-dimethoxybenzoic acid and subsequent transformations, submitted that to baker's yeast-catalyzed reduction and successfully obtained the hydroxyketone **2b′**. In turn, another approach via the alkylation of the precursors, 2-methylcycloalkane-1,3-diones, which apparently seems to be more general, is somewhat problematic. Toward most alkyl halides other than methyl iodide, the enolates of the diketones are prone to undergo O-alkylation even with ethyl iodide.[4] The allyl and propargyl groups meet this criterion, and the diketones **1c** and **1d** are obtainable in acceptable yields, but the subsequent yeast-catalyzed reductions proceeded in a nonenantiotopic group-selective manner to give an almost equimolar mixture of diastereomers (**2c**+**2c′**, **2d**+**2d′**, Scheme 1).[5,6] We

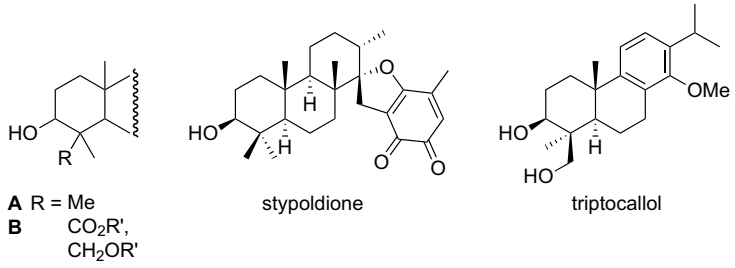

Figure 1. Characteristic structural feature with chiral centers in natural product synthesis, such as stypoldione and triptocallol.

Keywords: Substituted cyclohexanone; Substituted cyclopentanone; Hydroxyketone; Radical β-fragmentation.
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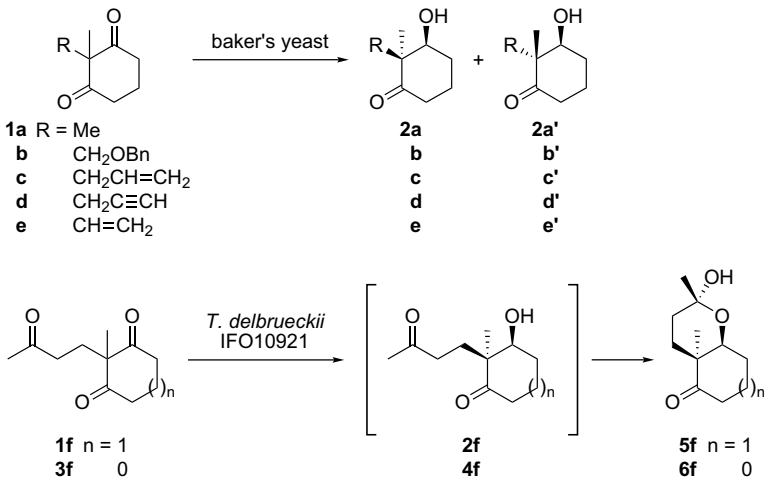


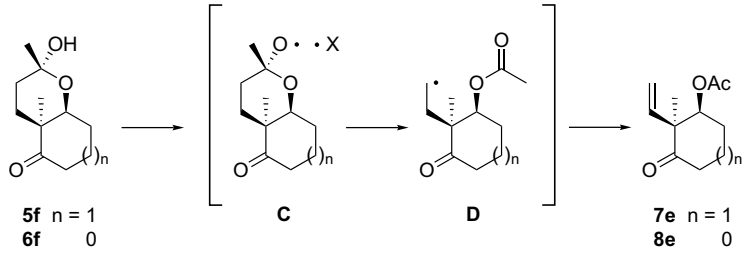
Scheme 1. Yeast-catalyzed reduction of 2-substituted-2-methylcycloalkane-1,3-diones.

envisioned that 2-methyl-2-vinylcycloalkane-1,3-diones such as **1e**, would be other very attractive substrates for yeast-catalyzed reduction. The direct introduction of a vinyl group on this position, however, is extremely difficult, and only phenyl 2-(trimethylsilyl)ethynyl sulfone as an electrophile, vinyl cation equivalent, has been reported.[7]

In recent years, we found that a yeast strain, *Torulaspora delbrueckii* IFO10921,[8] worked very well on the triketones **1f** and **3f**, which are readily available from 2-methylcycloalkane-1,3-diones and methyl vinyl ketone, to give the stereochemically pure products (Scheme 1).[8,9] For example, from the triketone **1f**, a cyclic hemiacetal **5f** was obtained in 60% yield. The combined X-ray crystallographic structure determination and chemical transformations proved its structure to be (1*S*,3*S*,6*S*)-configuration.[8]

In this paper, we report an unprecedented route to 3-acetoxy-2-methyl-2-vinylcyclohexanone **7e** and 3-acetoxy-2-methyl-2-vinylcyclopentanone **8e** in stereochemically pure state, from these cyclic hemiacetals **5f** and **6f** by means of a radical β-fragmentation. Our idea, which was inspired by Rigby's transformation,[10] is shown in Scheme 2. If a proper precursor can be prepared and the homolytic cleavage of this O–X bond takes place (**C**), the subsequent β-fragmentation will provide the radical intermediate (**D**). The oxidation of this species will give a 2-vinyl substituent in the desired product. This scheme may be advantageous in that a part of the original hemiacetal skeleton is incorporated into the protecting group of the liberated hydroxyl group, in the form of acetate.

Along this line, the reaction conditions were extensively examined (Table 1). In our first attempt for the use of



Scheme 2. Synthetic plan for 3-acetoxy-2-methyl-2-vinylcycloalkanones.

Table 1. Studies on the reagents available to the β-fragmentation of the hemiacetal **5f**[a]

Entry	Reagent	Oxidant	Yield (%)	Recovery (%)
1[b]	$Pb(OAc)_4$	$Cu(OAc)_2 \cdot H_2O$	12	—
2[c]	$PhI(OCOCF_3)_2$	$Cu(OAc)_2$	Decomposition	
3	$PhI(OAc)_2$	$Cu(OAc)_2$	30	10
4	PhI=O	$Cu(OAc)_2$	9	—

[a] Pyridine, benzene, reflux, 15 h.
[b] 38 h.
[c] CH_2Cl_2, rt, 1 h.

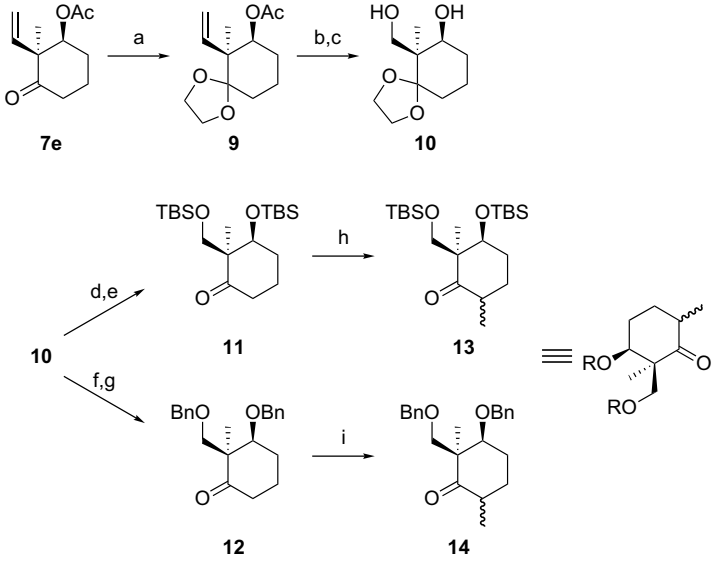
Table 2. Conditions for the β-fragmentation with iodobenzene diacetate[a]

Entry	Substrate	Additive	Solvent	Yield (%)	Recovery (%)
1	**5f**	—	Benzene	No reaction	
2	**5f**	Pyridine	Benzene	27	10
3	**5f**	2,2′-Bipyridyl	Benzene	9	43
4	**5f**	2,6-Lutidine	Benzene	30	10
5	**5f**	2,6-Lutidine	Cyclohexane	26	19
6	**5f**	2,6-Lutidine	$ClCH_2CH_2Cl$	16	16
7	**5f**	2,6-Lutidine	DME	13	34
8[b]	**5f**	I_2, hν	CH_2Cl_2	Decomposition	
9[c]	**5f**	2,6-Lutidine	Benzene	39	—
10[c]	**6f**	2,6-Lutidine	Benzene	65	—

[a] $PhI(OAc)_2$, $Cu(OAc)_2$, reflux, 15 h.
[b] $PhI(OAc)_2$, tungsten lamp (100 W), rt, 10 h.
[c] 5 mmol scale; $PhI(OAc)_2$ (20 mmol, five times), $Cu(OAc)_2$ (2.0 mmol, five times), 2,6-lutidine (6.0 mmol), benzene (100 mL), reflux, 5 h; for detail, see Ref. 14.

lead(IV) acetate and copper(II) acetate under Rigby's conditions,[10] however, only a trace amount of the desired product **7e** was obtained as a very complex mixture with a number of byproducts. Even after the extensive investigation on the reaction conditions with this radical initiator, the yield of **7e** remained as low as 12% (entry 1).

We turned our attention to the use of organohypervalent iodine reagents, by which a wide range of applications have been exploited in organic synthesis.[11] It has been known that a combined use of iodobenzene diacetate, pyridine, and a catalytic amount of copper(II) acetate equally worked well instead of the lead(IV)-mediated decarboxylative radical formation into alkene.[12] Through the studies with several candidates (entries 2–4), we selected iodobenzene diacetate, and based on the use of this reagent, the reaction conditions were further elaborated (Table 2). The excessively used iodobenzene diacetate itself did not work as the oxidant for the radical intermediate (**D**), and the use of copper(II) acetate was necessary (entry 1). As the substituents for another additive, pyridine (entry 2), which works as the ligand indispensable for the monomerization of the copper complex,[13] 2,2′-bipyridyl and 2,6-lutidine were compared (entries 3 and 4). The latter advantageous case was further studied by a change of the reaction solvent (entries 4–7), and the highest yield was given in benzene (entry 4). Although the yield of **7e** increased, this reaction produced a considerable amount of byproducts due to the side reactions, which occurred under the severe reflux conditions. In turn, a more mild photochemical initiation and the following trapping with iodine were attempted (entry 8), expecting to obtain a primary iodide, which would be led to the vinyl group by the subsequent dehydrohalogenation. To our disappointment, the multispots on TLC analysis were still observed. Among the many products, only an isolable but very unstable component showed an acetate of the partial structure by NMR, immediately after the



Scheme 3. Reagents and conditions: (a) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux (89%); (b) O_3, CH_2Cl_2, Me_2S; (c) $LiAlH_4$, Et_2O (2 steps 77%); (d) TBSCl, imidazole, DMF, 60 °C; (e) PPTS, acetone–H_2O, 60 °C (2 steps 75%); (f) BnBr, NaH, DMF; (g) *p*-TsOH, acetone–H_2O, 60 °C (2 steps quant); (h) LHMDS, HMPA, THF, −78 °C, then MeI (74%); (i) LHMDS, HMPA, THF, −78 °C, then MeI (quant).

purification. The component rapidly turned red by releasing iodine. Based on these evidences, we reasoned that the desirable β-fragmentation certainly occurred to give an iodide, but due to its unstable nature, further decomposition predominated. In contrast, we were pleased that under the optimized conditions[14] giving the highest yield of **7e** (39%, entry 9) from **5f**, the yield of the five-membered ring product **8e** was remarkably high (65%, entry 10) from the substrate **6f**. In this way, new stereochemically pure cyclohexanone **7e**[15] and cyclopentanone **8e**[16] were obtained.

We continued the functional group transformations toward the key synthetic intermediates of **B** as shown in Scheme 3. The carbonyl group of **7e** was protected as 1,3-dioxolane (**9**)[17] in 89% yield, and the ozonolysis of **9** followed by the reduction provided the diol **10**[18] in 77% yield from **9**. Both the TBS group (**11**)[19] and the benzyl group (**12**)[20] were effectively introduced in 75% yield and quantitative yield from **10**, respectively. This bis-benzyl ether **12** implies the successful approach to the diastereomeric synthetic equivalent of **2b′** reported by Nakada and co-workers.[3] Although these compounds (**11** and **12**) have three functional groups, all adjacent to the quaternary chiral center in a very congested manner, the methylation was successful to provide **13** and **14**, important synthetic intermediates for **B**, in 75% yield and quantitative yield as a diastereomeric mixture at the C-6 position (ca. 1:1 mixture), respectively.

In conclusion, a new entry to stereochemically pure forms of highly functionalized cycloalkanone intermediates for natural product synthesis, by means of a combination of yeast-catalyzed reduction and subsequent radical β-fragmentation as the key steps, was disclosed.

Acknowledgements

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14. A mixture of benzene (100 mL), $Cu(OAc)_2$ (2.0 mmol), and 2,6-lutidine (6.0 mmol) was stirred for 15 min at 60 °C, and the hemiacetal (5.0 mmol) was added. The reaction mixture was degassed by the repetitive evacuation and substitution with argon. The first portion of $PhI(OAc)_2$ (20 mmol) was then added, and the reaction mixture was stirred under reflux. To this reaction mixture, four additional portions of $PhI(OAc)_2$ and $Cu(OAc)_2$ (each 20 and 2.0 mmol, respectively) were added in an interval of every 1 h, and the mixture was stirred under reflux for a total of 5 h. The disappearance of the starting material was confirmed by TLC analysis (silica gel, developed with hexane–EtOAc 2:1). The reaction mixture was filtered through a pad of silica gel, and the filtrate was concentrated in vacuo. The residue was diluted with EtOAc, successively washed with saturated aqueous $Na_2S_2O_3$ solution, water, saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography.
15. **7e**: $[\alpha]_D^{19}$ +65.1° (*c* 1.07, $CHCl_3$). IR ν_{max} 1738, 1714, 1634, 1229 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.56–1.70 (1H, m), 1.83–2.06 (3H, m), 2.06 (3H, s), 2.36 (1H, dddd, $J = 1.0$, 4.4, 4.4, 14.7 Hz), 2.52 (1H, ddd, $J = 5.9$, 11.7, 14.7 Hz), 4.81 (1H, dd, $J = 3.9$, 9.8 Hz), 5.00 (1H, d, $J = 17.6$ Hz), 5.22 (1H, d, $J = 10.7$ Hz), 6.25 (1H, dd, $J = 10.7$, 17.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.4, 21.1, 26.9, 37.8, 56.6, 78.1, 116.9, 137.4, 170.0, 209.1. Anal. Found: C, 67.19; H, 8.35. Calcd for $C_{11}H_{16}O_3$: C,

67.32; H, 8.22. Based on the GLC analysis [column, TCI Chiraldex B-PM, 30 m × 0.25 mm × 0.125 μm; flow rate 50 mL/min; pressure 180 kPa; oven temperature 120 °C; an authentic specimen (±)-**7e**: t_R = 26.8 and 27.6 min], the β-fragmentation product **7e** of microbial origin coincided the peak of 26.8 min, and its ee was determined to be >99.9%. As, no racemization was observed in this β-fragmentation process, the absolute configuration of **7e** was unambiguously confirmed to be (2*S*,3*S*).

16. **8e**: $[\alpha]_D^{22}$ −25.7° (*c* 1.02, $CHCl_3$). IR ν_{max} 1743, 1638, 1242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.95–2.03 (1H, m), 2.07 (3H, s), 2.29–2.38 (2H, m), 2.44–2.56 (1H, m), 5.11–5.16 (2H, m), 5.25 (1H, d, J = 10.7 Hz), 5.86 (1H, dd, J = 10.7, 17.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.1, 25.5, 34.5, 55.4, 79.2, 117.4, 134.4, 170.1, 215.9. Anal. Found: C, 66.07; H, 7.83. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Based on the GLC analysis [column, Supelco BETA DEX™ 225, 30 m × 0.25 mm × 0.25 μm; flow rate 50 mL/min; pressure 180 kPa; oven temperature 120 °C; an authentic specimen (±)-**8e**: t_R = 15.4 and 15.8 min], the β-fragmentation product **8e** of microbial origin coincided the peak of 15.4 min, and its ee was determined to be >99.9%.
17. **9**: $[\alpha]_D^{25}$ +99.5° (*c* 1.35, $CHCl_3$). IR ν_{max} 1734, 1653, 1237, 1042 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.57–1.87 (6H, m), 2.03 (3H, s), 3.86–3.98 (4H, m), 4.89–4.98 (1H, m), 5.26 (1H, dd, J = 2.0, 11.2 Hz), 5.29 (1H, dd, J = 2.0, 17.6 Hz), 6.15 (1H, dd, J = 11.2, 17.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 19.5, 21.2, 26.6, 30.7, 50.0, 65.1, 65.2, 77.3, 111.6, 116.9, 137.9, 170.4. Anal. Found: C, 65.22; H, 8.55. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39.
18. **10**: $[\alpha]_D^{23}$ +13.0° (*c* 1.03, $CHCl_3$). IR ν_{max} 3324, 1453, 1190, 1132, 1100, 1044, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.49–1.80 (6H, m), 2.59 (1H, s), 3.13 (1H, s), 3.72–3.78 (2H, m), 3.89–4.03 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 18.3, 28.7, 29.9, 46.2, 63.9, 65.1, 65.3, 75.1, 112.9. Anal. Found: C, 59.46; H, 8.96. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97.
19. **11**: $[\alpha]_D^{20}$ +19.8° (*c* 0.89, $CHCl_3$). IR ν_{max} 1709, 1472, 1463, 1255, 1078, 837, 775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.03 (3H, s), 0.05 (3H, s), 0.05 (3H, s), 0.86 (9H, s), 0.88 (9H, s), 1.13 (3H, s), 1.62–1.71 (1H, m), 1.80–1.97 (2H, m), 1.99–2.09 (1H, m), 2.33 (1H, ddd, J = 5.9, 6.4, 14.2 Hz), 2.45 (1H, ddd, J = 5.9, 8.8, 14.6 Hz), 3.76 (1H, d, J = 9.8 Hz), 3.81 (1H, d, J = 9.8 Hz), 3.94 (1H, dd, J = 2.9, 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.2, −5.0, −4.2, 18.1, 18.3, 19.2, 20.5, 25.9, 26.0, 28.8, 38.3, 55.8, 64.4, 75.2, 214.0. Anal. Found: C, 62.31; H, 10.70. Calcd for $C_{20}H_{42}O_3Si_2$: C, 62.12; H, 10.95.
20. **12**: $[\alpha]_D^{20}$ +27.9° (*c* 1.07, $CHCl_3$). IR ν_{max} 3087, 3062, 3030, 1705, 1453, 1091, 1076, 736, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, s), 1.67–1.75 (1H, m), 1.94–2.10 (3H, m), 2.30 (1H, ddd, J = 5.4, 5.4, 14.6 Hz), 2.50 (1H, ddd, J = 5.9, 10.2, 14.6 Hz), 3.68 (1H, d, J = 9.3 Hz), 3.80 (1H, dd, J = 3.9, 4.4 Hz), 3.85 (1H, d, J = 9.3 Hz), 4.40 (1H, d, J = 11.7 Hz), 4.47 (1H, d, J = 12.2 Hz), 4.52 (1H, d, J = 12.2 Hz), 4.57 (1H, d, J = 11.7 Hz), 7.23–7.33 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.5, 24.0, 37.9, 54.4, 71.3, 71.7, 73.3, 81.6, 127.3, 127.3, 127.3, 128.2, 138.5, 213.1. Anal. Found: C, 78.00; H, 7.78. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74.