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Enantioselective formal synthesis of tridemethylisovelleral

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Abstract—A simple and efficient synthetic route to the bicyclic α,β-unsaturated β-keto ester methyl (3a*S*,7a*S*)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indene-5-carboxylate, a versatile intermediate in the synthesis of biologically active unsaturated 1,4-dialdehydes, is described. The synthesis includes a chirality introducing nonenzymatic asymmetric desymmetrization (ADS) reaction of a cyclic *meso*-anhydride **4** and a modified Hofmann method for preparing exocyclic dienes. The ester was synthesized in a moderate overall yield (19%) from **6** and with an excellent enantioselectivity (>90%).

(+)-Isovelleral (**1**), a thoroughly studied fungal metabolite found in the fruit bodies of *Lactarius vellereus*, possesses potent antimicrobial and cytotoxic activities.[1] The biological activities are linked to the presence of an unsaturated 1,4-dialdehyde moiety and a cyclopropane ring. The rationally designed synthetic racemic analog tridemethylisovelleral (**2**) proved to be an even more potent compound with antitumour properties in sub-nanomolar concentrations.[2] Because of these results we desired to prepare **2** in enantiomerically pure form since (+)-isovelleral and its stereoisomers have been shown to possess significantly different biological activities (Fig. 1).[1a] Inspired by the pseudo-C_2-symmetry of **2** (Scheme 1) we were interested in studying the possibility of utilizing a nonenzymatic asymmetric desymmetrization (ADS)[3] reaction in the synthesis of this compound. A symmetry-breaking hydrolytic opening of a *meso*-anhydride would lead to a non-racemic ester carboxylic acid. The *meso*-anhydride could be formed through a diastereoselective Diels–Alder reaction between a 1,3-diene and maleic anhydride. ADS reactions are powerful methods of establishing several stereocentres in a single symmetry-breaking operation. Considerable attention has been given to the use of prochiral cyclic anhydrides,[4] which are readily available through the Diels–Alder reaction of maleic anhydride and suitable dienes as substrates. The catalytic ADS of cyclic anhydrides often utilizes bis-cinchona derived catalysts[5] such as hydroquinine (anthraquinone-1,4-diyl) diether ($(DHQ)_2AQN$) and hydroquinidine (anthraquinone-1,4-diyl) diether ($(DHQD)_2AQN$).

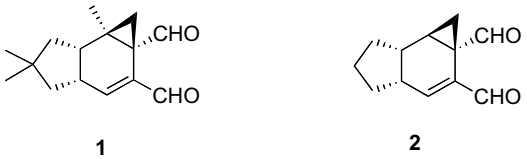

Figure 1.

This synthetic methodology could possibly also be used in the synthesis of other marasmanes or terpenoids with compounds such as **3** as key intermediates.

Preparation of the *meso*-anhydride for the ADS reaction required an efficient method for the synthesis of dimethylene compound **6**. Exocyclic 1,3-dienes are especially interesting and useful compounds, but have proven to be quite difficult to prepare since they easily rearrange to more substituted conjugated alkenes. Exocyclic dienes are usually formed via a Hofmann elimination,[6] or by some other pyrolysis reaction,[7] but can also be synthesized via vinylogous Peterson olefination,[8] E2-elimination[9] and allene dimerization.[10] A prerequisite for the Hofmann elimination is the presence of a hydroxide counter-ion, which is usually obtained from the corresponding halide with moist silver oxide. Ion-exchange resins have in some cases[11] been used instead of silver oxide to effect ion exchange, since the oxide is light sensitive and expensive. The resins themselves are quite expensive too, but they are very stable and recyclable.

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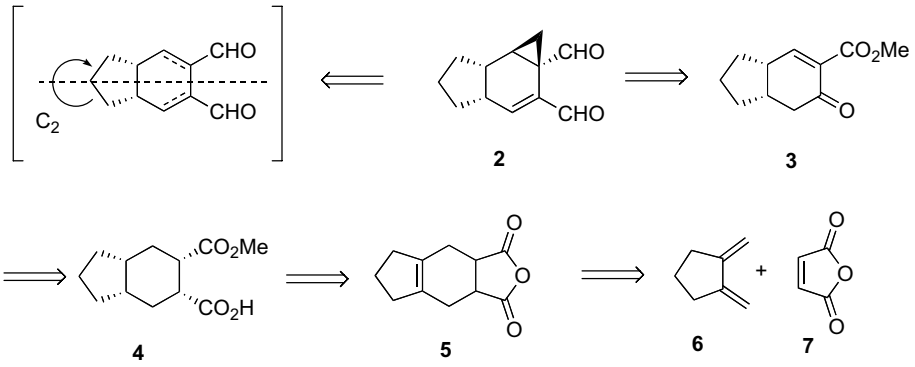
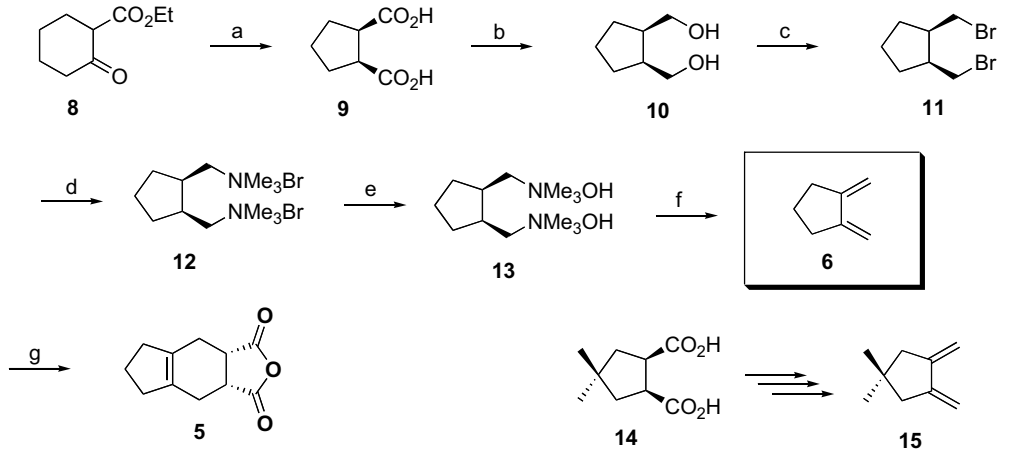


Scheme 1. Retrosynthetic analysis.

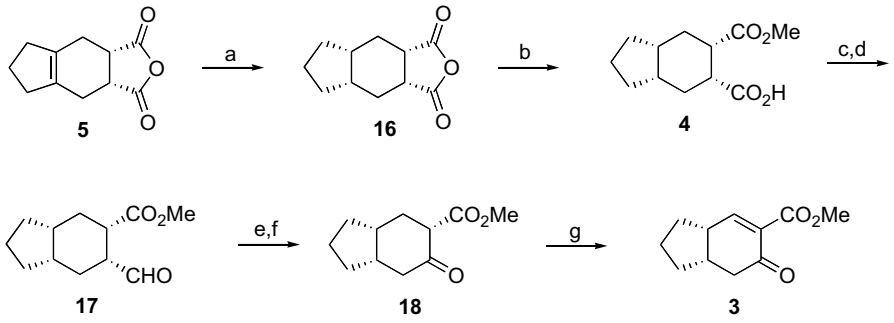
As a part of this project we were interested in exploring the formation of exocyclic dienes without the use of silver reagents.

The synthesis of the dienes studied in this investigation began with the bromination of β-keto ester **8**, which in turn was subjected to a Favorskii rearrangement and recrystallized to give diacid **9** in a 74% yield (Scheme 2).[12] Diacid **9** was then converted directly to diol **10** with borane dimethyl sulfide complex in the presence trimethylborate.[13] Treatment of crude **10** with phosphorus tribromide gave crude **11**, which was immediately converted into the bis-quaternary ammonium bromide **12**[7a] with an excess of ethanolic trimethylamine at 100 °C. The bromide counter-ion was exchanged for hydroxide using a strong basic ion-exchange resin (DOWEX 550A OH). The resin was activated prior to use and could be used again after regeneration.[14] Thermal decomposition of the bis-quaternary ammonium hydroxide **13** gave the desired diene **6** in an acceptable yield. The presence of the diene was confirmed by NMR and by preparation of the Diels–Alder adduct with maleic anhydride. Crude **6** was reacted with maleic anhydride in benzene at room temperature to provide *meso*-anhydride **5** in an excellent yield. 1,1-Dimethyl-3,4-bis-methylene-cyclopentane (**15**) was prepared in an analogous manner from the corresponding diacid (**14**).

In order to convert **5** into ketoester **3**, the carbon–carbon double bond had to be reduced (Scheme 3). Although tetra-substituted alkenes are known to be resistant towards standard hydrogenation conditions, substrates similar to **5** have been reduced with Adam's catalyst in dry THF.[15] These conditions effected the desired reduction with an excellent stereoselectivity and without any ring opening or reduction of the cyclic anhydride to afford **16**. There are several ADS-catalysts available, however, many are required in stoichiometric amounts. The catalyst $(DHQD)_2AQN$ is effective even at low concentrations (<10 mol %) and was considered for the desired transformation.[4] In the event, the $(DHQD)_2AQN$-catalyzed ADS methanolysis of **16** afforded **4** in more than 90% enantiomeric excess[16] and in a good yield. Mono-acid **4** was then conveniently converted into the corresponding acid chloride with oxalyl chloride in toluene with a constant purge of nitrogen, to remove produced hydrochloric acid. Subsequent catalytic hydrogenation with Pd/C and 2,6-lutidine, used to lower the catalyst activity, in THF at 40 psi and room temperature[17] afforded aldehyde **17**, which was directly converted to the corresponding trimethylsilylenol ether.



Scheme 2. Reagents and conditions: (a) (i) Br_2, $CHCl_3$, 0 °C to rt, overnight; (ii) KOH, H_2O, 0 °C to rt, 74%; (b) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to rt, overnight; (c) PBr_3, −10 °C → rt → 85 °C, overnight; (d) NMe_3 (33% in EtOH), sealed tube 100 °C, overnight, 47% from **10**; (e) DOWEX 550A OH, H_2O; (f) pyrolysis, 200 mmHg, 130–200 °C, 30% from **12**; (g) maleic anhydride, benzene, rt, 2 d, 99%.



Scheme 3. Reagents and conditions: (a) Pt_2O, H_2 (1 atm), THF, rt, overnight; (b) $(DHQD)_2AQN$, MeOH, Et_2O, −18 °C, 3 d; (c) $(COCl)_2$, toluene, rt, overnight; (d) Pd/C, H_2 (40 psi), 2,6-lutidine, THF, overnight; (e) $ZnCl_2$, Et_3N, TMSCl, benzene, rt (0.5 h) to 40 °C, overnight; (f) O_3, MeOH/CH_2Cl_2 (4:1), −7 °C, 39% from 5; (g) (i) PhSeCl, pyridine, CH_2Cl_2, 0 °C, 0.5 h; (ii) 35% H_2O_2, CH_2Cl_2, 0 °C, 0.5 h, 48%.

Attempts to form the silylenol ether by conventional methods, for example, using a base and then chlorotrimethylsilane, failed. However, enolization of aldehyde **17** in the presence of chlorotrimethylsilane using triethylamine-zinc chloride complex[18] was successful, and the product was immediately ozonolyzed[19] to yield β-keto ester **18** in a 39% yield and 6 steps from **5**. Introduction of the α,β-unsaturation in **18** to yield α,β-unsaturated β-keto ester **3** was done as previously described[2] using PhSeCl and hydrogen peroxide. Keto ester **3** was obtained in a 90% enantiomeric excess[20] and **3** has previously been transformed to the target dialdehyde **2** in a 25% overall yield.[2]

In summary, we have developed a facile method for the asymmetric synthesis of an important intermediate in the synthesis of biologically active dialdehydes utilizing a nonenzymatic asymmetric desymmetrization (ADS) reaction. We have also shown that reactive exocylic dienes can be readily synthesized from quatenary amines using recyclable ion-exchange resins, eliminating the need for expensive silver salts.

Acknowledgement

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20. *Methyl (3aS,7aS)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indene-5-carboxylate* (**3**). PhSeCl (201 mg, 1.05 mmol) was dissolved in CH_2Cl_2 (30 ml) and cooled to 0 °C. Pyridine (89 μl, 1.10 mmol) was added and the orange

solution turned yellow. The resulting mixture was stirred for 15 min at 0 °C and **18** (191 mg, 0.97 mmol) in CH_2Cl_2 (3.5 ml) was added. The solution was stirred for an additional 15 min. The reaction mixture was washed with 2 M aqueous HCl (2 × 15 ml), cooled to 0 °C and 35% aqueous H_2O_2 (70 μl) was added. An additional amount of H_2O_2 (70 μl) was added after 10 min and again after 20 min. After a further 10 min, H_2O (10 ml) was added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$, dried, concentrated and chromatographed to give **3** (75 mg, 0.39 mmol, 48%) and recovered **18** (32 mg, 0.16 mmol, 17%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (1H, m), 1.68 (1H, m), 1.71 (2H, m), 1.87 (1H, m), 2.07 (1H, m), 2.48 (1H, m), 2.60 (1H, m), 2.62 (1H, m), 2.94 (1H, m), 3.82 (3H, s), 7.49 (1H, d, $J = 3.8$ Hz); ^{13}C NMR $CDCl_3$ (100 MHz) δ 24.3, 30.6, 31.1, 37.9, 40.2, 41.5, 52.2, 131.1, 158.8, 165.1, 194.9; HRMS (FAB): for $C_{11}H_{15}O_3$ calcd 195.1021 $[M+H]^+$; found 195.1030. $[\alpha]_D^{20}$ −52 (*c* 0.04, $CHCl_3$).