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Synthesis of (*dl*)-Trichodiene Using Novel Ring Transformation Reaction

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Key Words (dl)-trichodiene, fragmentation reaction, ethylene glycol, ring cleavage, quaternary center

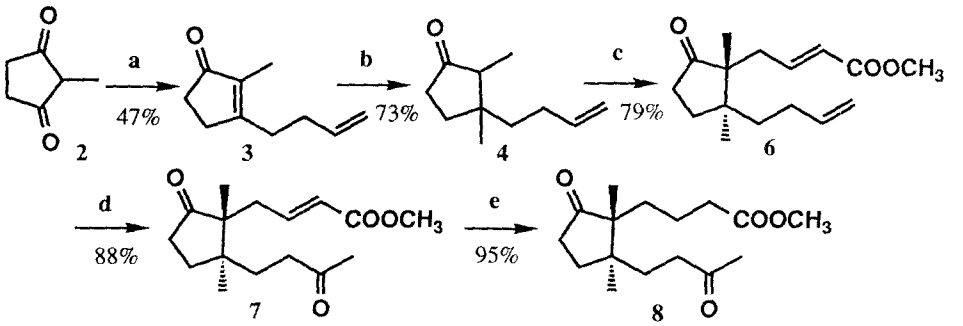
Abstract: Synthesis of (dl)-trichodiene has been completed via novel ring transformation reaction using TsOH / ethylene glycol

Ring transformation reaction is one of the most important tools to construct a synthetically difficult skeleton, because this reaction provides a new route to prepare the target molecule from another readily prepared compound.

Recently, we reported the novel ring cleavage and reconstruction reactions[1] of cyclic ketones. By treatment with BF_3 / ethylene glycol (acetalization conditions), cyclopentanones and cyclohexanones with the carbonyl function at the C_3- or C_4-position of the α- and β-side chains underwent ring cleavage to build up new five, six, and/or seven-membered rings. The reaction process involving aldol condensation, acetalization and Grob fragmentation[2] was tentatively proposed. These novel ring transformation reactions were applied to the syntheses of natural products such as bulnesol[1b] and acorenone B[1f].

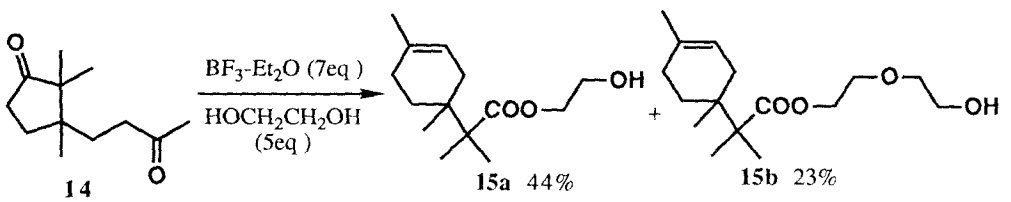
In this communication, we wish to describe the new application of this novel ring transformation reaction to the synthesis of (*dl*)-trichodiene (**1**). Trichodiene **1** is a bicyclic sesquiterpene, and is an important biosynthetic precursor of trichotecenes[3], which possess antifungal, antitumor and cytotoxic biological activities. Up to now, extensive effort has been directed to the synthesis of trichodiene[4], because of its synthetically attractive structure associated with the presence of two adjacent quarternary centers in the molecule, and because trichodiene is found only in minute amount in fungus *Trichothecium roseum*. The approach (Scheme 3) employing novel ring transformation reaction as the key step seems to be synthetically advantageous for the introduction of the two adjacent quaternary centers.

Commercially available, the 1,3-diketone (**2**)[5] could be readily converted to the enone (**3**) *via* a two-step sequence [i) *sec*-BuOH, H^+; ii) butenyl magnesium bromide]. Treatment of **3** with MeCu-BF_3 / Et_2O (-78 °C - r.t.)[6,7] afforded the expected 1,4-adduct (**4**). The adduct **4** was converted to the ester (**6**) with two adjacent quaternary centers *via* three sequences[8] [i) TMSCl / Et_3N, 130 °C; ii) $LiNH_2$; iii) methyl 4-iodocrotonate, -60 °C]. The ^1H NMR spectrum of **6** indicated the presence of two methyl ester protons (δ: 3.733, 3.731), suggesting a mixture of stereoisomers of 2,3-*trans*-and *cis*-cyclopentanones in the ratio of 2 (*trans*) to 1 (*cis*). The cyclopentanone (**6**) could then be converted to the diketone (**8**) with the two quaternary centers required for ring transformation reaction *via* Wacker oxidation to the unsaturated-diketone (**7**) followed by H_2 / Pd-C reduction of olefinic function[9] (Scheme 1).



(a) i) *sec*-BuOH, H^+; ii) butenyl magnesium bromide (b) MeCu-BF_3 / Et_2O
(c) i) TMSCl / Et_3N, 130°C; ii) $LiNH_2$, iii) methyl 4-iodocrotonate
(d) $PdCl_2$, CuCl, H_2O, O_2 (e) H_2 / Pd-C **Scheme 1**

The feasibility of ring transformation reaction was preliminarily examined by using a model compound (**14**)[10] with two adjacent quaternary centers (Scheme 2). By treatment with BF_3 (7eq) / ethylene glycol (5eq) in CH_2Cl_2 at room temperature[11], this substrate underwent facile ring transformation to afford the products (**15a,b**). The structure of each product was determined by the analysis of spectroscopic data The IR and ^1H NMR spectrum of **15a** indicated the existence of OH (3450 cm^{-1}), ester (1720 cm^{-1}) function, and allylic-CH_3 [δ: 1.63 (3H, s)], $COOCH_2CH_2O$ [δ· 3 70-3.90 (2H, m) and 4 10-4.20 (2H, m)], olefinic proton [δ· 5.25 (1H, m)], respectively, in addition to MS spectrum [m/z 222 (M^+-H_2O), 205, 178, 107]. The ^1H NMR spectrum of **15b** showed the presence of $COOCH_2CH_2OCH_2CH_2O$ [δ. 3 50-3.70 (6H, m) and 4 15-4 25 (2H, m)]



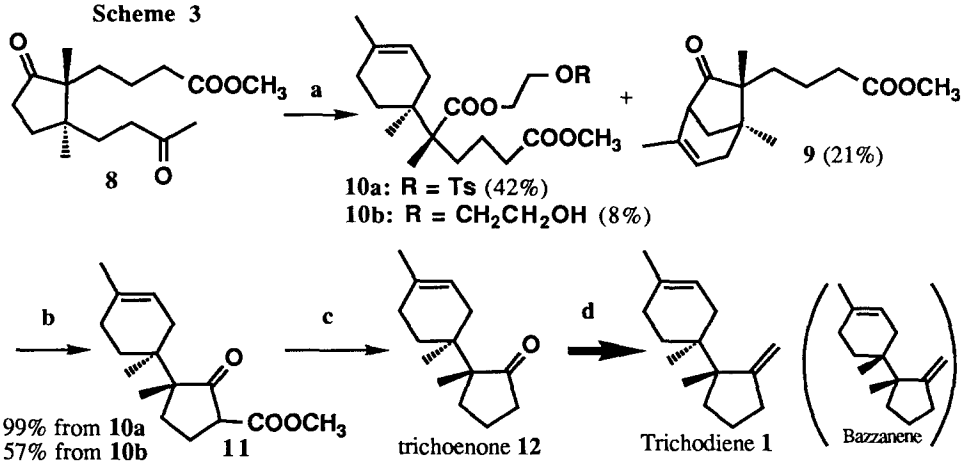
Scheme 2

With the success of the model study, we turned our attention to the synthesis of trichodiene **1** (Scheme 3). The diketone **8** was subjected to fragmentation conditions using BF_3 / ethylene glycol. However, no fragmentation product was obtained, and only aldol condensation product (**9**) was obtained in 56% yield This result may be ascribed to the bulky substituents at the α-position of cyclopentanone; that is to say, the employed reaction conditions are too weak for the acetalization of a hindered carbonyl function.

The difficulties in ring transformation using BF_3 / ethylene glycol could be overcome by employing the reaction conditions of TsOH-H_2O (2eq) / ethylene glycol (5eq) in refluxing benzene. According to this procedure, the ring transformation products (**10a**, **b**) were obtained in 42% and 8% yields, in addition to the aldol condensation product (**9**) (21%). The structures of these products were determined by ^1H NMR, IR and MS spectroscopic data. The ^1H NMR spectrum of **10a** indicated the presence of *p*-tolyl function [δ: 2 46 (3H, s); 7.34 (2H, d, *J*=10 Hz); 7.78 (2H, d, *J*=10 Hz)], olefinic proton [δ 5 23 (1H, m)], ethylene glycol ester [δ. 4 23

(4H, s)], methyl ester [δ: 3.66 (3H, s)], and allylic methyl proton [δ: 1.63 (3H, br s)]. The IR spectrum [carbonyl (1705 cm^{-1})] and MS spectrum [m/z: 480 (M^+)] also supported the proposed structure.

Scheme 3



(a) $TsOH\text{-}H_2O$ (2eq.) / $HOCH_2CH_2OH$ (5eq.) (b) $NaN(SiMe_3)_2$ (4eq.)
(c) DBU, 2,4,6-collidine (d) *ref.* 4b,c

Each product was converted to the β-keto ester (**11**) (99% yield from **10a**, 57% yield from **10b**) by treatment with $NaN(SiMe_3)_2$ (4eq, r.t.). According to the Welch procedure[4b] (DBU in 2,4,6-collidine at 180 °C for 3h), the β-keto ester **11** was transformed into trichoenone (**12**) in 78% yield[12]. Spectroscopic data of trichoenone were identical with those reported by Welch *et al*[4b]. The ^1H NMR spectrum of **12** indicated that this material is a 2:1 mixture of trichoenone and its diastereomer, bazzanenone[4b] [δ: 0.894, 0.907 (total-3H, each s); 1.009, 1.019 (total-3H, each s)]. In the synthesis[4b] of trichodiene **1** from **12** by Wittig reaction using methylenetriphenylphosphorane, it is already known that bazzanenone was not converted to bazzanene under the same conditions[4b]. Furthermore, trichodiene **1** can be separated[4c] from its diastereomer, bazzanene, by $AgNO_3$ impregnated silica gel chromatography. Thus, a formal synthesis of (*dl*)-trichodiene **1** was achieved.

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5 1,3-Diketone **2**; 2-Methyl-1,3-cyclopentanedione is available from Aldrich Chemical Company.

6. 1,4-Addition by Gilman reagents or Grignard reagent in the presence of CuI and/or CuBr resulted in failure.

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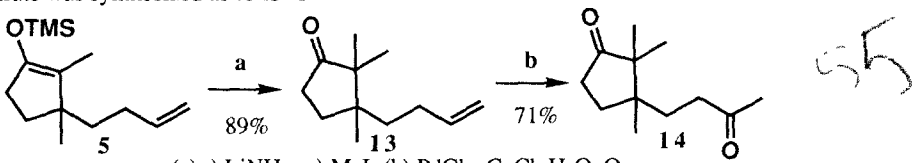
9. Selected spectroscopic data of each compound. All compounds were obtained as colorless oil.

4· IR· 1735, 1640 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 5 60-6 00 (1H, m), 4.85-5 10 (2H, m), 0.80-1.15 (6H, m) MS m/z. 166 (M^+), 94. bp 90-100 °C (bath temp.) / 0.3 mmHg

6: IR: 1720, 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 6.85-7 15 (1H, m), 5 75-5.95 (2H, m), 4.95-5 10 (2H, m), 3.731, 3.733 (total-3H, each s), 0 92, 0.95 (total-6H, each s). MS m/z 264 (M^+), 178, 43

8: IR: 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.657, 3.664 (total-3H, each s), 2 179, 2.192 (total-3H, each s), 0.842, 0.903, 0.932, 0.960 (total-6H, each s). MS m/z: 282 (M^+), 264, 111.

10. Substrate was synthesized as follows



(a) i) $LiNH_2$, ii) MeI, (b) $PdCl_2$, CuCl, H_2O, O_2

11. Selected spectroscopic data of preliminary experimental products. All compounds were obtained as colorless oil.

14: IR: 1735, 1715 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 2 91 (3H, s), 2.10-2 50 (4H, m), 0.94 (6H, s), 0.86 (3H, s). MS m/z: 196 (M^+), 178, 43

15a: IR: 3450, 1720 cm^{-1} ^1H NMR ($CDCl_3$) δ: 5 25 (1H, m), 4.10-4.20 (2H, m), 3.70-3.90 (2H, m), 1.63 (3H, br s), 1.18 (3H, s), 1.15 (3H, s), 0.89 (3H, s). MS m/z· 222 (M^+-H_2O), 205, 178, 107. **15b**. IR: 3450, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.25 (1H, m), 4.15-4.25 (2H, m), 3 50-3.70 (6H, m), 1 63 (3H, br s), 1.17 (3H, s), 1.14 (3H, s), 0.88 (3H, s). MS m/z. 222 (M^+), 205, 178, 107

12. Spectroscopic data of compounds. All compounds were obtained as colorless oil

9: IR· 1730 cm^{-1} ^1H NMR ($CDCl_3$) δ 5 30-5 38 (1H, m), 3 657, 3.663 (total-3H, each s), 2 60 (1H, m), 1.70 (3H, br s), 1.006, 1.023, 1.057, 1 094 (total-6H, each s) MS m/z. 264 (M^+), 107.

10a: IR: 1705 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ. 7.78 (2H, d, *J*=10 Hz), 7.34 (2H, d, *J*=10 Hz), 5.23 (1H, m), 4.23 (4H, s), 3.66 (3H, s), 2 46 (3H, s), 1 63 (3H, br s), 0 819, 1 046, 1 096 (total-6H, s). MS m/z: 480 (M^+), 448, 172 **10b** IR. 3500, 1740, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ. 5.25 (1H, m), 4.10-4 30 (2H, m), 3.66 (3H, s), 3.50-3.75 (6H, m), 1.62 (3H, br s), 0.87, 1.11, 1 15 (total-6H, each s) MS m/z. 371 (M^++1).

11: IR: 1750, 1725, 1660, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ· 5.27 (1H, m), 3.73, 3.75 (total-3H, each s), 1.63 (3H, br s), 1.09 (3H, s), 0 91 (3H, s). MS m/z 264 (M^+), 164

12. IR: 1725 cm^{-1} ^1H NMR ($CDCl_3$) δ. 5.28 (1H, m), 1 63 (3H, br s), 1.009, 1.019 (total-3H, each s), 0.894, 0.907 (total-3H, each s) MS m/z 206 (M^+)

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