Highly Stereoselective Synthesis of Trisubstituted γ,δ-Unsaturated Acid and Aldehyde *via* Ketal Claisen Rearrangement

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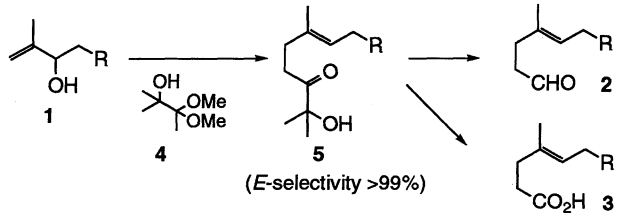
A new sequence for the highly stereoselective (*E*>99%) synthesis of a trisubstituted γ,δ-unsaturated acid (**3**), which consists of a ketal Claisen rearrangement of a terpene allylic alcohol with 2,2-dimethoxy-3-methyl-3-butanol and a subsequent oxidative cleavage of the resulting α-ketol, is applicable even to the preparation of **3** which is difficult to synthesize by traditional methods. The related procedure for preparation of the corresponding aldehyde is also described.

Trisubstituted γ,δ-unsaturated acid **3** has frequently been used as a key intermediate in total synthesis of a natural product[1] and is contained in the partial structure of mycophenolic acid,[1d,1e] which is now of great interest as an immunosuppressant. Hydrolysis of orthoester Claisen rearrangement product (*E*-selectivity: usually 96-7%)[2] of allylic alcohol **1** offers one of the most promising procedures for the preparation of **3**.[1a-c] Unfortunately, however, this procedure cannot be applied to the synthesis of **3** containing groups which are easily hydrolyzable, and removal of the Z-isomer formed is also generally difficult unless recrystallization of **3** is possible. The Ireland Claisen rearrangement of the acetate of **1** is known to provide **3** of higher *E*-selectivity (>99%).[3] However, it is not applicable to **1** having groups reactive to a base, e.g., allylic esters.

We recently reported that a ketal Claisen rearrangement of **1a** with 2,2-dimethoxy-3-methyl-3-butanol (**4**) proceeded highly *E*-selectively (>99%) to give an isoprene unit elongation product, α-ketol **5a**, in high yield,[4] from which marine cembranoids were successfully synthesized *via* both enantiomers of an allylic alcohol[5] and trisubstituted γ,δ-unsaturated aldehyde **2a**.[4] We further investigated the synthetic application of the α-ketol **5**, and in this communication describe a new sequence for the highly stereoselective (*E*>99%) synthesis of **3** utilizing **5**.



Allylic alcohol **1** was heated with **4** (3.5 equiv.) in the presence of 2,4-dinitrophenol (2 mol%) at 130 °C for 5 h while the methanol formed was distilled off (conditions A).[4] Important protective groups frequently used in natural products syntheses, THP, acetyl, *tert*-butyldimethylsilyl, and ethyleneketal, present in **1** were unaffected during the reaction. The desired α-ketol **5** was obtained in high yield after column chromatographic purification.

In the case of **1g** and **1h**, which possess an extra hydroxyl group, brief exposure of a crude reaction product to acid (cat. TsOH in MeOH) was required before the purification. This treatment was omitted when the reaction was performed with a small excess of **4** (1.2 equiv.) using H_3PO_4 (2 mol%) as the catalyst in refluxing toluene through Molecular Sieves 4A, though a longer reaction time (12-24 hr) was required (conditions B).[7]

Subsequent $NaIO_4$ (1.3 equiv.) oxidation of **5** in aqueous methanol at room temperature followed by usual workup gave the corresponding **3** in a good yield as a sole acidic product without further purification (Table 1). Although none of the *Z*-isomer was

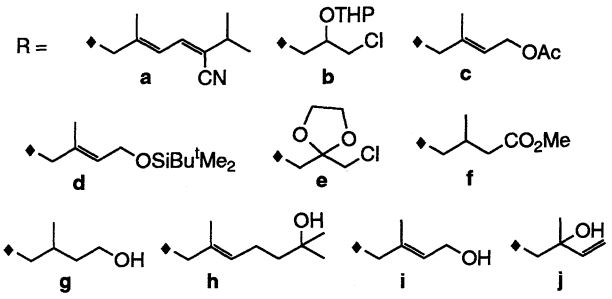


Table 1. Synthesis of aldehyde **2** and acid **3** from **1**

Substrate	Reaction conditions[a]	Product	Yield (%)[b]		
1a	A	-		**2a**[c]	83
1a	B	**5a**	91	**3a**	65
1b[d]	A	-		**2b**	68
1c	A	-		**2c**[e]	78
1c	A	**5c**	81	**3c**	69
1d	A	-		**2d**	75
1e[d]	A	-		**2e**	70
1e	A	**5e**	85	**3e**	73
1f	A	**5f**	93	**3f**	72
1g	B	-		**2g**	78
1g	B	**5g**	89	**3g**	79
1h	B[f]	-		**2h**	70
1i	A[g, h]	**5i**	39	**2i**	33[i]
1i	A[g, h]	**5i**	39	**3i**	84
1j	A[h]	**5j**	77	**2j**	71[i]
1j	A[h]	**5j**	77	**3j**	69

[a] See text. [b] Isolated yields. Yields for **2** are overall yield from **1**. For the synthesis of **2**, which was purified by SiO_2 column chromatography, the intermediates, **5** and its reduction product, α-diol, were not isolated. [c] Ref. 4. [d] Ref. 1a. [e] Ref. 6. [f] 2,4-Dinitrophenol (2 mol%) was used instead of H_3PO_4, which gave a ca. 1 : 2 mixture of **5h** and its dehydration products (exo/endo = ca. 2/1). Reaction time: 24 h. [g] Reaction temp.: 120 °C. Unreacted **1i** was recovered (12%). [h] The acid treatment was carried out before isolation of **5**. [i] α-Ketol **5** was isolated.

detected by ^{1}H-NMR (500 MHz) analysis of **3** thus obtained,[8] **5a-d** were converted to the corresponding aldehyde **2a-d**[4] in order to determine the *E*-selectivity of the sequence by capillary GLC analysis.[9] The results confirmed *E*>99% in all cases. Thus, this simultaneously signified a sequence, which is equivalent to the Claisen rearrangement, using **5** as generally applicable for the highly stereoselective preparation of **2**. These results are also summarized in Table 1.

It is noteworthy that **3c** was successfully synthesized from **1c** which possesses an allylic acetate, a substrate for Ireland Claisen rearrangement. It is also difficult to prepare a half ester of dicarboxylic acid, **3f**, from **1f** *via* orthoester Claisen rearrangement. In the present sequence, the pathway for the formation of carboxylic acid functionality is oxidative cleavage of α-ketol, which is different from those of the traditional procedures, and this made it possible to synthesize **3c** and **3f**.

We found that geraniol (**6**) reacted with **4** more slowly than **1**. Only about 10% of rearrangement product **8** was formed under the reaction conditions A. Reaction at a higher temperature ultimately provided **8** in a satisfactory yield (Table 2). By contrast, linalool (**7**) was completely unreactive even under the latter conditions. When H_3PO_4[10] was used instead of 2,4-dinitrophenol as the catalyst, however, the desired **9** was eventually obtained (Table 2). These results are presumably explained by the increase of steric repulsion in **6** during conversion of the transition state of rearrangement to the product, in which a quaternary carbon center is newly formed. This is supported by the fact that the intermediates of rearrangement, ketal **10** and enol ether **11**[11] were isolated, though in impure forms due to their instability. In contrast with **6**, formation of the intermediate may be retarded owing to steric bulkiness of a tertiary alcohol in **7**.

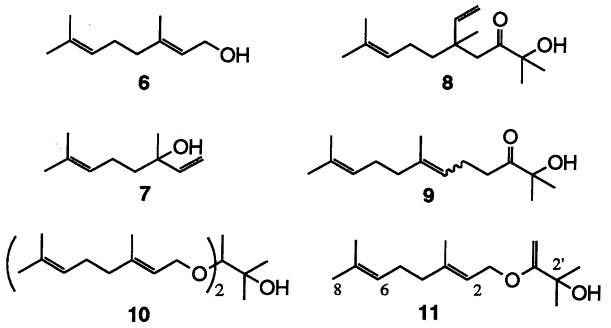


Table 2. Ketal Claisen rearrangements of **6** and **7** with **4**

Substrate	Catalyst[a]	Temp[b]	t/h	Product	Yield (%)[c]
6	DNP	130	5	**8**	8[d]
6	DNP	165	10	**8**	82
7	DNP	165	10	**9**[e]	0[f]
7	H_3PO_4	130	12	**9**	65

[a] 2 mol%. DNP = 2,4-dinitrophenol. [b] Bath temperature. [c] Isolated yield. [d] The brief acid treatment (MeOH, cat. p-TsOH) was performed prior to SiO_2 column chromatography to hydrolyze **10** and **11**. [e] Z/E = ca. 3/4, determined by GLC analysis. [f] Unreacted **7** was recovered in 89% yield.

On the basis of the above results, we applied the present sequence to substrates possessing two different types of allylic alcohols in the molecules to demonstrate its synthetic versatility. As expected, the regioselective reaction products, acids **3i**, **3j**, and aldehydes **2i**, **2j**, were obtained respectively (Table 1).

In summary, the terminal α-ketol isoprenoid **5**, which is prepared from **1** by the ketal Claisen rearrangement using **4**, can be oxidized with $NaIO_4$ to afford γ,δ-unsaturated acid **3** with higher *E*-selectivity (>99%) than that obtained *via* orthoester Claisen rearrangement. Furthermore, this sequence even gave **3**, which is difficult to synthesize by traditional methods, and therefore provides an alternative and useful route for the preparation of **3**.

References and Notes

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7 A few percent of unreacted **1** was detected by GLC analysis.

8 By ^{1}H-NMR analysis, Z-isomer (3%) in an orthoester Claisen rearrangement product could be unequivocally detected in a separate experiment.[1a]

9 The Claisen rearrangement of vinyl ethers of **1a-d** was performed in order to identify the Z-isomer by capillary GLC (in refluxing toluene, *E*-selectivities: 88-89%).

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11 The relative ratio of these compounds in a crude reaction product was estimated by ^{1}H-NMR analysis as **8** : **10** : **11** = ca. 1 : 6 : 3. NMR (300 MHz) data: δ_H **10**, 1.23 (6H, s, 2'-Me), 1.32 (3H, s, 1'-Me), 1.60 and 1.63 (each 6H, each s, 3- and 7-Me), 1.68 (6H, *J* 0.7 Hz, 8-H), 2.0-2.2 (8H, m, 4- and 5-H), 4.07 and 4.19 (each 2H, each dd, *J* each 12.0, 6.5, 1-H), 5.10 (2H, m, 6-H), 5.34 (2H, bt, *J* 6.9, 2-H); **11**, 1.38 (6H, s, 2'-Me), 1.61, 1.67 and 1.69 (each 3H, each s, 3- and 7-Me, 8-H), 2.0-2.2 (4H, m, 4- and 5-H), 3.91 and 4.21 (each 1H, each d, *J* each 2.6, CH_2=C), 4.25 (2H, d, *J* 6.5, 1-H), 5.11 (1H, m, 6-H), 5.39 (1H, bt, *J* 6.5, 2-H).