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# Preparation of Optically Active (4aα,8aβ)-Octahydro-4a-methyl-8-methylene-2(1H)-naphthalenone, a Key Intermediate for the Enantioselective Synthesis of Eudesmane Sesquiterpenes

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The titled optically active methylene ketone was prepared in 45% ee from 3-methyl-1,2-cyclohexanedione by use of a novel asymmetric Michael addition with (R,R)-(-)-2,3-butanediol as chiral auxiliary.

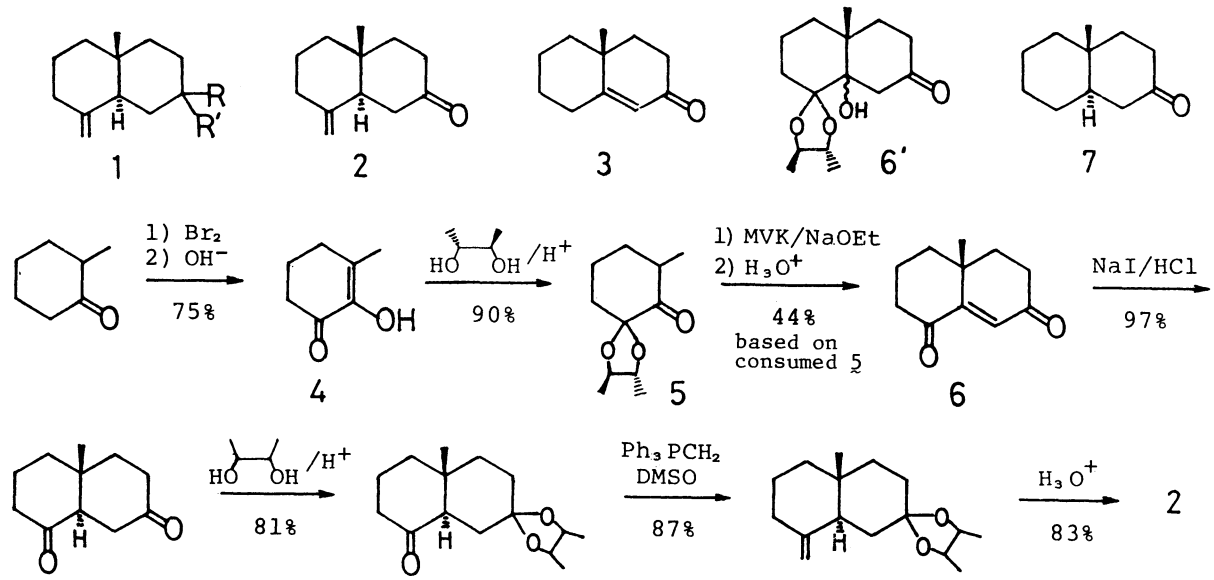
The first total synthesis of eudesmane sesquiterpenes 1 demonstrated by Marshall et al.[1] in 1965 included the titled racemic methylene ketone 2 as the key intermediate which was prepared from 2-methylcyclohexanone and methyl vinyl ketone via an enone 3. This method has been accepted widely[2] and Wijnberg et al. have succeeded in improving the functional group transformation from 3 to 2.[3] An important problem is, however, the fact that the key intermediate 2 has never been obtained in an optically active form. It seems very difficult to conduct an asymmetric Michael addtion between the enolate of 2-methylcyclohexanone and methyl vinyl ketone.

We introduce here a novel method for the preparation of 2 by use of 3-methyl-1,2-cyclohexanedione, which is simple and is capable of producing the optically active form. The reaction sequence is shown in Scheme 1.

2-Methylcyclohexanone was converted easily to the enol of 3-methyl-1,2-cyclohexanedione (4) in 75% yield according to the method reported.[4] Acetalization of 4 with (R,R)-2,3-butanediol (1.15 equiv.) was achieved selectively by refluxing in benzene with a minimum amount of *p*-TsOH to give 5 in 90% yield. The α-keto acetal 5 dissolved in NaOEt(0.1 equiv.)/EtOH reacted with methyl vinyl ketone (1.5 equiv.) at -15→-5 °C for 23 h to give the annelation product 6' in 43% yield and the starting 5 in 32% recovery.[5] Then 6' was treated with aqueous HCl to give enedione 6 in 69% yield. The asymmetric Michael addition was carried out at various temperatures as shown in Table 1.

The configuration of the carbon-4a was determined as R after conversion to ketone 7 ($[\alpha]_D$ -17° (c 0.8, $CHCl_3$)) (lit.[6] $[\alpha]_D$ +33° (c 1.14, $CHCl_3$) for the S configuration), which is in agreement with the stereochemistry of asymmetric induction presumed in Fig. 1. The enedione 6 was transformed to 2[7] ($[\alpha]_D$ -23.9° (c 1.17, $CHCl_3$)) in 56% yield according to the sequence shown.

This is the first asymmetric synthesis of optically active 2, though the % ee remains to be improved. Further elaboration of the asymmetric induction is now in progress in our laboratory.



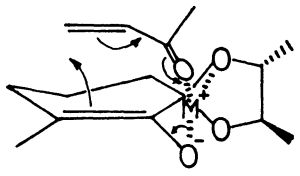

Scheme 1.

Table 1. Asymmetric Michael Addition of α-Keto Acetal 5 with Methyl Vinyl Ketone Leading to Annelation Product 6' and Enedione 6[a)]

| | | 6' | | | 5 | 6 | | | |
|---|---|---|---|---|---|---|---|---|---|
| Temp/°C | Time/h | Yield/% | $[\alpha]_D$/° | (c)[b)] | Recovd/% | Yield[c)]/% | $[\alpha]_D$/° | (c)[b)] | ee/%[d)] |
| 25 | 2.5 | 78 | -5.4 | (1.00) | 12 | 83 | +24.0 | (1.15) | 30 |
| -5—15 | 23 | 64 | -5.0 | (1.21) | 19 | 69 | +34.7 | (1.17) | 42 |
| -15—-5 | 23 | 43 | -4.2 | (1.01) | 32 | 69 | +39.0 | (0.97) | 45 |
| -15—-10 | 48 | 29 | -5.4 | (1.03) | 39 | 75 | +35.1 | (0.81) | 42 |

a) Methyl vinyl ketone 1.5 equiv.; NaOEt(0.1 equiv.)/EtOH. b) In $CHCl_3$. c) The yield for 6'→6. d) Determined by $^1H$ NMR using the signal of =CH- with $Eu(hfc)_3$.

Fig. 1. The asymmetric induction in Michael addition. The (R) configuration is formed.



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