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Intramolecular Ene Approach to Stereocontrolled Synthesis of Cyclopentanoids

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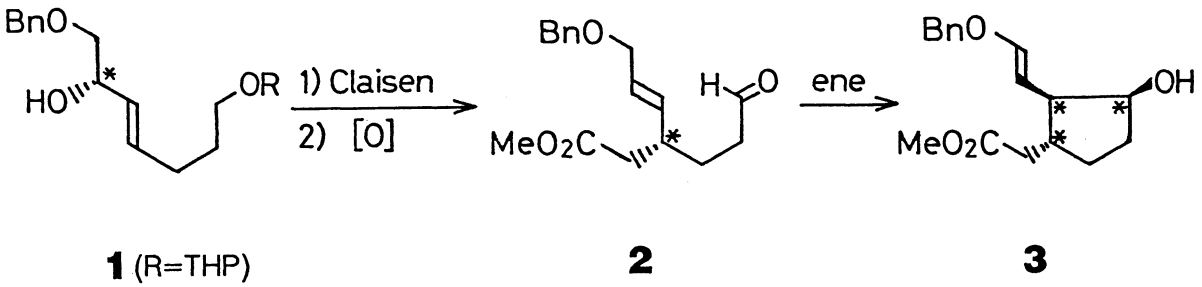
A new and stereoselective approach to cyclopentanoid synthesis is described. The key step is the thermal intramolecular ene reaction of 4-carbomethoxymethyl-7-benzyloxy-5-heptenal, prepared by the Claisen rearrangement, to afford the 2,3-disubstituted cyclopentanol derivative in a highly stereoselective fashion.

The development of synthetic methods for cyclopentanoids has still attracted much interest in recent years.[1] As part of the research program to develop the intramolecular ene reaction into a general and stereocontrolled strategy for carbocyclization, we have recently described a sequential Claisen-ene approach to the stereocontrolled synthesis of a steroid C/D ring synthon, where an acetylenic bond acts as the internal enophile.[2] Herein we wish to report an intramolecular ene approach for stereocontrolled synthesis of cyclopentanoids, where aldehyde functionality is used as the internal enophile.

Scheme 1 illustrates our basic strategy. Its key feature is that the requisite ene substrate **2** can be derived via the Johnson-Claisen rearrangement of the easily available allylic alcohol **1**. Thus, a major problem in this strategy is the stereochemistry of the ene cyclization process (**2** ⟶ **3**).

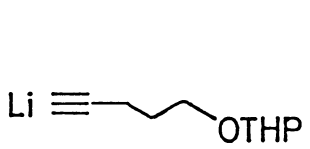


1 (R=THP) **2** **3**

Scheme 1.

The starting alcohol (±)-**1** (Claisen substrate) was prepared by addition of the acetylide **4** to benzyloxyacetaldehyde (-78 °C, Et_2O) followed by trans-reduction ($LiAlH_4$, THF) in 54% yield.[3] The Claisen rearrangement of **1** ($CH_3C(OCH_3)_3$, 2,6-xylenol, 220 °C, 18 h) afforded 92% yield of the unsaturated ester **5** with a high

geometrical purity (100% E).[4] Deprotection (p-TsOH, MeOH) followed by oxidation (pyridinium chlorochromate, CH_2Cl_2) gave the ene substrate **2** in 53% isolated yield.[3]



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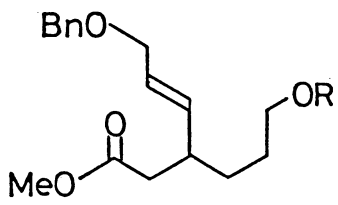
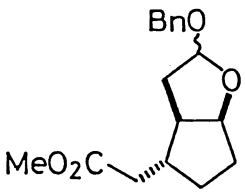


5, R=THP ; **6**, R=H

The crucial ene reaction of **2** was found to proceed at 220 °C but did not go to completion even for three days.[5] Interestingly, what we obtained was not the expected ene product **3** but a mixture of the bicyclic compounds **7**[6] and **8**,[7] along with the recovery of **2** and benzyl alcohol. It thus appears that the ene product **3** once formed undergoes spontaneously the intramolecular addition of the hydroxy group to the enol ether moiety to give the bicyclic acetal **7** from which benzyl alcohol is eliminated to afford the bicyclic enol ether **8**. Direct hydrolysis of the resulting mixture (1 M HCl, 25 °C) followed by column chromatography furnished the cyclopentanolactol **9** as single product in 92% isolated yield (based on reacted **2**), along with 48% recovery of **2**.[8]

The stereochemistry of the lactol **9** was assigned to 1,2-cis, 2,3-trans on the basis of NMR comparison of its lactone **10**[9] prepared via the Jones oxidation of **9** (78% yield) with the known 3-epimer.[10] Thus, the present ene cyclization is now proved to proceed with an exceptionally high diastereo (1,2-cis) and diastereofacial (2,3-trans) selectivity.[11]



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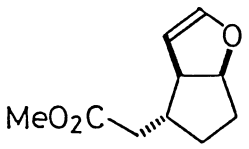

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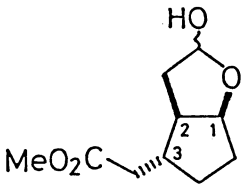

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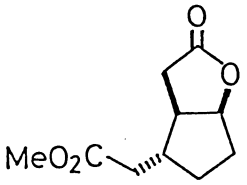

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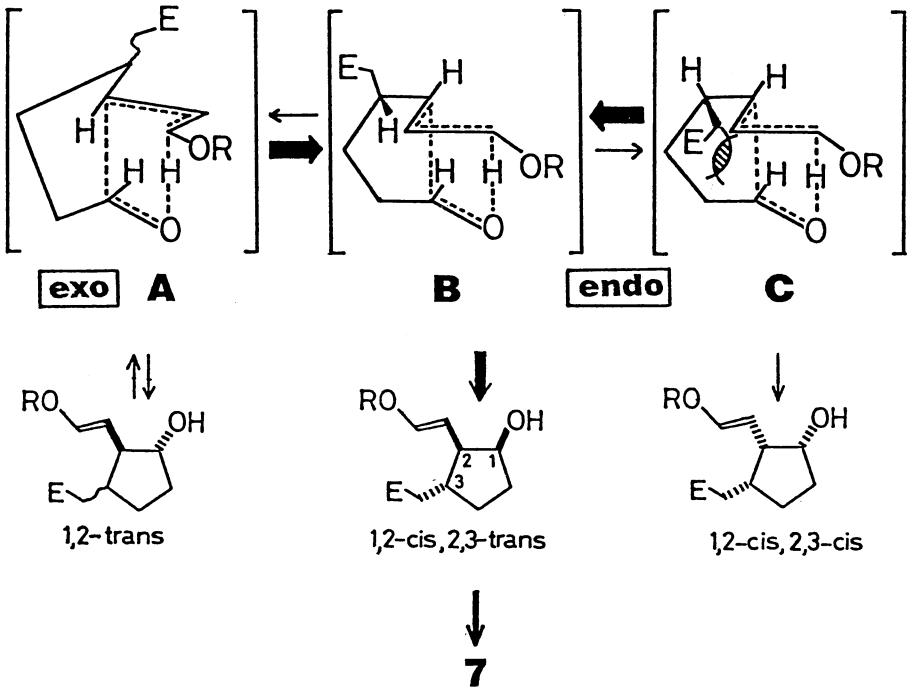
These high stereoselectivities observed in the present ene cyclization can be explained as follows. The exclusive formation of the 1,2-cis configuration is rationalized by assuming the involvement of the retro-ene reaction as shown in Scheme 2. The 1,2-cis ene product (**3**) once formed can be cyclized to the thermodynamically stable acetal **7**, while the 1,2-trans counterpart formed via the exo-folded transition state **A** cannot be further cyclized but might undergoes the retro-ene reaction. The high 2,3-trans selectivity, on the other hand, can be visualized

by the endo-folded transition state **B** which is sterically less congested than the other endo-transition state **C**.



Scheme 2.

In order to demonstrate the synthetic utility of the present ene cyclization, we carried out the transformation of the lactol **9** to methyl (±)-jasmonate (**12**).[12] Thus, **9** was subjected to the Wittig olefination (n-$PrPPh_3^+Br^-$, n-BuLi, THF) to give the cyclopentanol **11** in 61% yield, however, as a geometrical mixture (Z/E = 68 : 32).[13] The Jones oxidation of **11** afforded **12** in 72% isolated yield.[14]

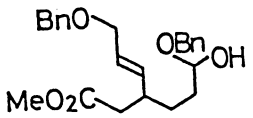
11 **12**

In summary, we have developed a new and stereocontrolled approach to cyclopentanoids based on the intramolecular carbonyl-ene reaction. The overall transformation outlined here, although made in racemic form, would be applicable to the synthesis of the optically active form, since the optically active form of the stating alcohol **1** is easily available from (S)- or (R)-glyceraldehyde and the complete transfer of chirality via the Claisen rearrangement is well established.[15] Further work along this line is now in progress in our labolatory.

We are grateful to Professor T. Kitahara (Univ. of Tokyo) for providing us with authentic samples of methyl jasmonate and its 2-epimer and for his helpful discussions. This work was supported in part by the Foundation "Hattori-Hokokai" and Grand-in-Aid for Encouragement of Young Scientist from the Ministry of Education, Science and Culture (No. 62750792).

References

1) B. M. Trost, Chem. Soc. Rev., 11, 141 (1982).
2) K. Takahashi, K. Mikami, and T. Nakai, Tetrahedron Lett., 29, 5277 (1988).
3) The overall yield has not been optimized yet.
4) **6**: IR (neat) 970 cm^{-1}; ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 30.0, 30.6, 38.6, 39.8, 51.3, 62.2, 70.3, 71.6, 127.3, 127.4, 127.5, 128.2, 135.9, 138.2, 172.6.
5) At 200 °C no ene-cyclization proceeded. Furthermore, attempted cyclizations using a Lewis acid such as Me_2AlCl, $MeAlCl_2$, $SnCl_4$, BF_3Et_2O, and $ZnBr_2$ failed.
6) **7**: ^1H NMR δ 3.70 (s, 3H, $-CO_2CH_3$), 4.48 and 4.72 (AB, 2H, J=12.6 Hz, $-OCH_2C_6H_5$), 4.70 (m, 1H, -OCH<), 5.30 (m, 1H, $-CH(O-)_2$), 7.43 (m, 5H, $-CH_2C_6H_5$).
7) **8**: ^1H NMR δ 3.72 (s, 3H, $-CO_2CH_3$), 4.8-5.2 (m, 1H, -OCH=CH-), 6.33 (m, 1H, -OCH=CH-).
8) This incompleteness of the present cyclization might be due largely to the partial destruction of the aldehyde functionality by the benzyl alcohol once formed through the formation of the hemiacetal (**13**).



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9) **10**: IR (neat) 1770, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.69 (s, 3H, $-CO_2CH_3$), 4.98 (m, 1H, -OCH<); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 30.7, 31.9, 35.1, 38.7, 42.7, 45.0, 51.8, 86.1, 173.1, 177.6.
10) H. Tanaka and S. Torii, J. Org. Chem., 40, 462 (1975).
11) For the diastereoselectivities in the five-membered ene cyclization, see the Reviews: W. Oppolzer and V. Snieckus, Angew. Chem., Int. Ed. Engl., 17, 476 (1978); D. F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions," Springer-Verlag, Berlin (1984).
12) Torii and Tanaka (Ref. 10) has already reported the multi-step conversion from the 3-epimer of **9** into methyl jasmonate, in which the Z-side chain was introduced via the Wittig reaction in a highly stereoselective fashion.
13) The low stereoselectivity is rather surprising in view of the relatively high Z-selectivity previously reported for the closely related reactions: see Ref. 10 and L. Crombie and K. M. Misty, J. Chem. Soc., Chem. Commun., 1988, 539.
14) **12**: IR (neat) 1730, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 0.95 (t, 3H, J=7.2 Hz, CH_3CH_2-), 3.70 (s, 3H, $-CO_2CH_3$), 5.40 (m, 2H, -CH=CH-).
15) R. K. Kill, "Chirality Transfer via Sigmatropic Rearrangement," in "Asymmetric Synthesis," ed by J. D. Morisson, Academic Press, Orlando, FL (1984), Vol. 3B, p. 503.

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