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SEQUENTIAL CLAISEN-ENE APPROACH TO CARBOCYCLIZATION: A NEW ENTRY TO A STEROID C/D RING SYNTHON

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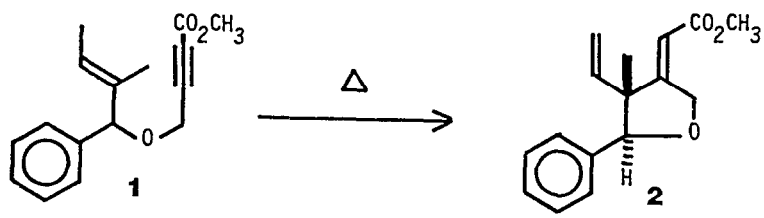
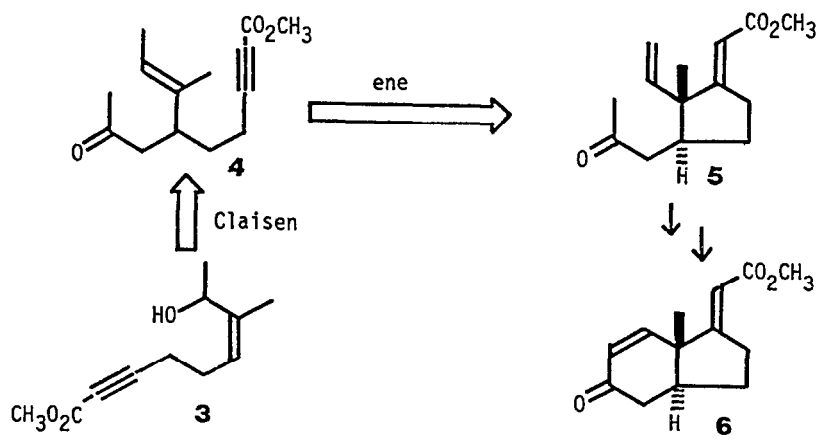
Summary: A new and facile entry to a steroid C/D ring synthon is described which relies on the sequential combination of the Claisen rearrangement with the intramolecular ene reaction involving an acetylenic bond with methoxycarbonyl group as the enophile.

The intramolecular ene reaction has currently been emerging as one of efficient tools for carbocyclization.[1] Recently we have reported that the thermal ene cyclization of the crotyl propargyl ether **1** can create a quarternary center in a highly diastereoselective fashion (eq 1).[2] This observation prompted us to apply this ene cyclization methodology to the synthesis of a steroid C/D ring synthon.[3] Scheme 1 illustrates our basic strategy which we now describe in this communication. Its key feature is that the requisite ene substrate **4** can be easily derived via the Claisen rearrangement. Thus, an intriguing problem in this strategy is whether the Claisen-ene sequence[4] can be achieved in tandem or not.

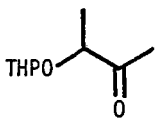


(1)

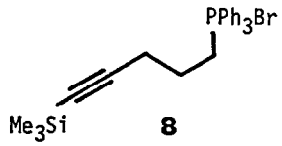
Scheme 1



The requisite alcohol **3** (Claisen substrate) was prepared from the protected acetoin **7** in a straightforward manner. Thus, **7** was subjected to the Wittig reaction using the phosphonium salt **8**[5] under the standard condition [n-BuLi, THF, -78 °C] to afford 76% yield of enyne **9** with extremely high stereoselectivity (>98% Z).[6] Enyne **9** was then converted to the Claisen substrate **3** in 84% yield by the standard three-step operation [n-Bu_4NF, THF; n-BuLi/$ClCO_2CH_3$, THF; p-TsOH, CH_3OH].



7



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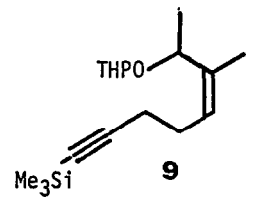
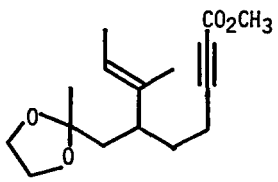


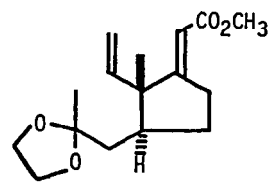
9

With a large quantity of **3** in hand, we first attempted the Claisen rearrangement with iso-propenyl methyl ether [$Hg(OAc)_2$, 170 °C, 2 days], with the hope that the Claisen product **4** spontaneously undergoes the intramolecular ene reaction to yield the desired cyclization product **5**. We found that the Claisen-ene sequence did occur in tandem to give **5** only in 29% yield and with low stereoselectivity (trans/cis = 6 : 4).[7,8] This low yield may be attributed to concurrent occurrence of the other type of ene reactions involving the carbonyl group of the Claisen product **4**.[9]

On the basis of these observation, we next carried out the ene reaction after protection of the carbonyl group of the Claisen product once isolated. Thus, the Claisen rearrangement was carried out at a lower temperature [100 °C, 1 day] followed by ketalization [$HOCH_2CH_2OH$, p-TsOH, benzene] to afford ketal **4a** in 71% overall yield. The ketal **4a** was then subjected to the ene cyclization [toluene, 170 °C, 90 h] to give the cyclization product **5a** in an increased yield (86%) as expected. Deprotection [p-TsOH, acetone] of **5a** gave rise to the desired methyl ketone 5 with enhanced stereoselectivity (trans/cis = 8 : 2).[7]

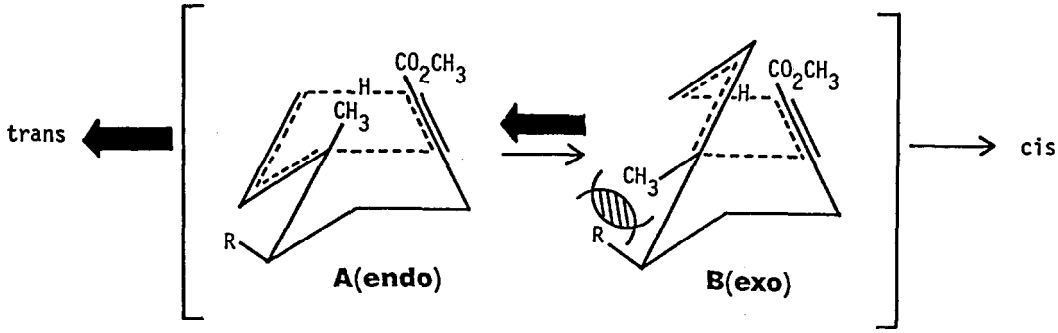


4a



5a

Of particular interest is the significant increase in diastereoselectivity observed in the ene cyclization of the ketal **4a** relative to the ketone **4**, which is readily explicable as follows. Of the two possible transition states **A** (**endo**) and **B** (**exo**),[11] the former leading to the trans-configuration is sterically more favorable because the latter could suffer the steric repulsion between CH_3 and R, depending on the bulkiness of R. Thus, the presence of the relatively bulky ketal moiety in **4a** is apparently responsible for the enhanced trans-selectivity.



Finally, the diastereomeric mixture of the ene product **5** was converted to the steroid C/D ring synthon **6** via the selective ozonolysis [O_3, pyridine, CH_2Cl_2, $(CH_3)_2S$] followed by the intramolecular aldol condensation [CH_3ONa, benzene]. Column chromatographic purification [SiO_2, hexane/AcOEt = 5 : 1] of the resulting stereomixture furnished the pure trans-isomer **6**[12] in 32% overall yield from **5a**. It should be noted that this steroid C/D ring synthon **6** possesses the unique multifunctionality which is useful for further construction of A/B ring as well as a side chain.

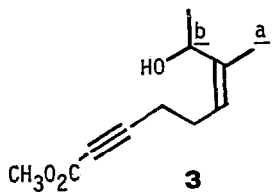
In summary, we have demonstrated that the ene cyclization methodology, combined with the Claisen rearrangement, provides a unique and facile entry to the steroid C/D ring synthon. The overall transformation outlined here, although made in racemic form, could be applicable to the synthesis of the optically active form starting with optically active acetoin, since the Claisen rearrangement concerned is well established to attain specific transfer of chirality along the acyclic array.[13] Further work along this line is under way in our laboratory.

Acknowledgment: This work was supported in part by Grand-in-Aid for Encouragement of Young Scientist from the Ministry of Education, Science and Culture, Japan (No. 62750792).

REFERENCES AND NOTES

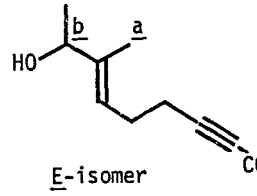
1. Reviews: a) W. Oppolzer and V. Snieckus, Angew. Chem. Int. Ed. Engl., 17, 476 (1978); b) D. F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions", Springer-Verlag, Berlin (1984).
2. K. Mikami, K. Takahashi, and T. Nakai, Chem. Lett., 1987, 2374.
3. For leading more recent references on the syntheses of steroid C/D ring synthon: a) T. Money and J. H. Hutchinson, J. Chem. Soc. Chem. Commun., 1986, 288; b) J. H. Hutchinson, T. Money, and S. Piper, ibid., 1984, 455; c) G. Stork, J. D. Winkler, and N. A. Saccomano, Tetrahedron Lett., 24, 465 (1983); d) K. Yamamoto, M. Iijima, Y. Ogimura, and J. Tsuji, Tetrahedron Lett., 25, 2813 (1984).
4. A similar type of tandem Claisen-ene sequence involving a simple olefin as the enophile has been reported: F. E. Ziegler and J. J. Mencel, Tetrahedron Lett., 25, 123 (1984); F. E. Ziegler and K. Mikami, ibid., 25, 127 (1984).
5. The phosphonium salt **8** was prepared in 38% overall yield from 4-pentyn-1-ol by the standard three-step method [EtMgBr, Me_3SiCl; TsCl, pyridine; PPh_3, 110 °C].
6. Still has reported that the salt-free Wittig reaction of an α-alkoxy ketone in the

presence of HMPA proceeds with high Z-selectivity: C. Streekumar, K. P. Durst, and W. C. Still, J. Org. Chem., 45, 4260 (1980). In the present Wittig reaction of **7**, however, a high Z-selectivity (>98%) was observed either with or without the use of HMPA. The Z-configuration of **9** was confirmed by ^{13}C NMR comparison of the alcohol **3** with its E-isomer independently prepared by Kishi's method: G. Schmidt, T. Fukuyama, K. Akasaka, and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979).



3

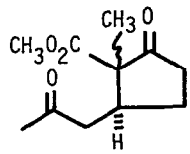
^{13}C NMR (ppm)
δ Ca: 19.13
Cb: 65.15



E-isomer

δ Ca: 11.76
Cb: 72.87

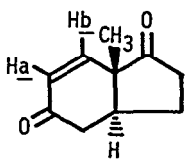
7. The configuration of the major isomer was assigned to trans on the basis of the transformation of **5a** [$LiAlH_4$; SO_3-pyridine/$LiAlH_4$; $RuCl_3$-$NaIO_4$; CH_2N_2; p-TsOH, acetone] to the known compound **10** whose stereochemistry is established.[3c]



10

^1H NMR (200 MHz, $CDCl_3$)
Major isomer (trans-**10**) : δ 0.86 (s, CH_3-C≡),
2.13 (s, CH_3CO-), 3.74 (s, CH_3CO_2-).
Minor isomer (cis-**10**) : δ 1.03 (s, CH_3-C≡),
2.17 (s, CH_3CO-), 3.69 (s, CH_3CO_2-).

8. We also found that a similar Claisen-ene sequence triggered by the Johnson type rearrangement [$CH_3C(OCH_3)_3$, H^+, 200 °C, 17 h] did occur, but in a poor yield (16%) and with low selectivity (70% trans).
9. For example, intramolcular ene reactions involving an enol as the ene component[10] and/or involving the carbonyl group as the enophile[1a] are conceivable.
10. Review: J. M. Conia and P. LePerchec, Synthesis, 1975, 1.
11. A similar transition state model has been proposed for the intramolecular ene reaction depicted by eq. 1.[2]
12. **6**: ^1H NMR 1.08 (s, CH_3-C≡), 5.90 (d, J = 10 Hz, COCH=CH), 7.30 (d, J = 10 Hz, COCH=CH); the trans configuration of **6** was confirmed by its ^1H NMR comparison with the closely related trans C/D ring synthon shown below[3d].



^1H NMR (ppm)
δ CH_3: 1.11
Ha: 5.94
Hb: 7.33

13. R. K. Hill, "Chirality Transfer via Sigmatropic Rearrangements", in "Asymmetric Synthesis", ed. J. D. Morrison, Academic Press Orland, FL (1984), Vol. 3B, p. 503.

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