CHEMISTRY LETTERS, pp. 1379-1382, 1983.

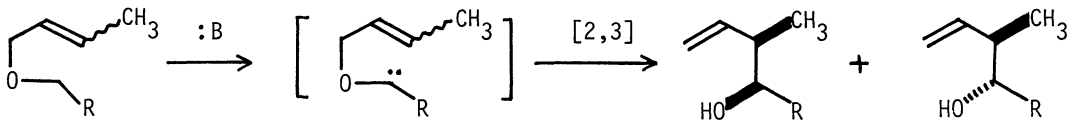
ENHANCEMENT OF ERYTHRO-SELECTIVITY IN THE [2,3]-WITTIG REARRANGEMENT OF CROTYL PROPARGYL ETHER SYSTEM AND ITS USE IN THE STEREOCONTROLLED FORMAL SYNTHESIS OF (±)-OUDEMANSIN

Kōichi MIKAMI, Ken-ichi AZUMA, and Takeshi NAKAI*

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

The [2,3]-Wittig variant of (Z)-crotyl ether involving trimethylsilylethynyl (or 1-propynyl) group as the key substituent on the carbanion terminus exhibits an exceptionally high level of erythro-selection, and its synthetic potential is illustrated in the formal synthesis of antibiotic (±)-oudemansin.

In continuing efforts to develop the [2,3]-Wittig sigmatropic rearrangement into a new basic strategy for acyclic stereocontrol,[1] we have recently reported the levels of diastereoselection in a broad range of [2,3]-Wittig variations with different substituents (R) on the carbanion terminus (Eq. 1)[2] and, on the basis of these, proposed a transition-state model[2d] that may serve as a guiding principle for designing highly diastereoselective modifications.

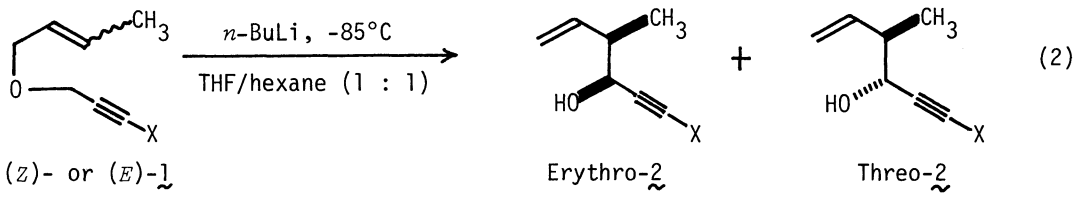


(Z) or (E) Erythro Threo

While the rearrangement of (E)-crotyl propargyl ether (1a, R = C≡CH) has been found to exhibit an extremely high (essentially 99%) threo-selectivity, the (Z)-counterpart provides 88-90% of erythro-selectivity which is not high enough for synthetic use.[2a] In view of the great importance of erythro β-methyl alcohols as intermediates for natural product synthesis, the enhancement of erythro-selectivity in this particular variant is highly desirable. Herein we report that the use of modified ethynyl groups, such as trimethylsilylethynyl or 1-propynyl, as the key substituent (R) remarkably enhances the erythro-selectivity, and illustrate its synthetic potential through the stereocontrolled formal synthesis of (±)-oudemansin.

At the outset, pertinent analysis of our transition-state model[2d] led us to expect that the introduction of a bulky group on the ethynyl moiety of 1a could improve the diastereoselectivity. Thus, we carried out the rearrangement of geometric pairs of 1b (X = $SiMe_3$)[3] and 1c (X = CH_3)[3]

under the standard conditions[2a] (Eq. 2). The erythro/threo ratio for 2b was determined after its conversion to 2a[4] via protodesilylation (CsF (0.03 equiv.), aqueous methanol, 50°C). The stereochemical assignment of 2c and the determination of its stereoisomeric ratio were made by analogous methods to those reported for 2a.[2a,5] The results are summarized in Table 1.



(Z)- or (E)-1 Erythro-2 Threo-2 (2)

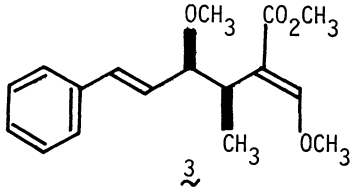
Table 1.

Entry	Substrate (geometric purity)[a]	Erythro : Threo[b]	Yield/%[c]
1[d]	(Z)-1a, X=H (98%)	88 : 12 (90 : 10)	56
2[d]	(E)-1a (93%)	7 : 93 (1 : 99)	61 (76)
3	(Z)-1b, X=$SiMe_3$ (93%)	98 : 2 (100 : 0)	74
4	(E)-1b (93%)	75 : 25 (73 : 27)	72
5	(Z)-1c, X=CH_3 (98%)	98 : 2 (100 : 0)	55 (74)
6	(E)-1c (93%)	8 : 92 (1 : 99)	65 (78)

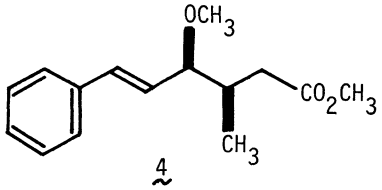
[a] Refers to the geometric purity of the starting crotyl alcohol. [b] Determined by GLC assay (PEG 20M). Values in parentheses refer to the calculated values based on 100% of geometric purity. [c] Distilled yields, not optimized yet. Values in parentheses refer to the GLC yields. [d] Cited from Ref. 2a.

Inspection of the data in Table 1 reveals significant stereochemical features of the present [2,3]-Wittig modifications. (1) The most striking is the remarkable enhancement of erythro-selection by the introduction of the silyl group (entry 3); surprisingly enough, the observed degree slightly exceeds the geometric purity of the substrate used. (2) (E)-1b exhibits the opposite sense of stereoselection to those of (E)-1a and -1c, though the level is not so high; this anomaly is apparently responsible for the exceedingly high erythro-selectivity described above. (3) (Z)- and (E)-1c show an enhanced erythro- and threo-selectivity, respectively; the both degrees are nearly equal to the geometric purities of the substrates employed. Regardless of the exact origin of the pronounced effects of the added groups on the diastereoselectivity,[6] the highly stereoselective [2,3]-Wittig variants provide the synthetic chemist with powerful weapons with which to attack the current problem of acyclic stereocontrol.

With the successful development of the highly erythro-selective [2,3]-Wittig varinats, our efforts were directed toward the total synthesis of oudemansin (3), an antibiotic isolated from mycella cultures of *Oudemansilla mucida*.[7] Thus, we carried out the stereocontrolled conversion of erythro-2a obtained above to ester 4 that has recently been established as an excellent precursor of (±)-3 by Oishi and co-workers.[8] Scheme 1 outlines the synthetic sequence in which the specific multifunctionality present in 2a is fully exploited.[9]



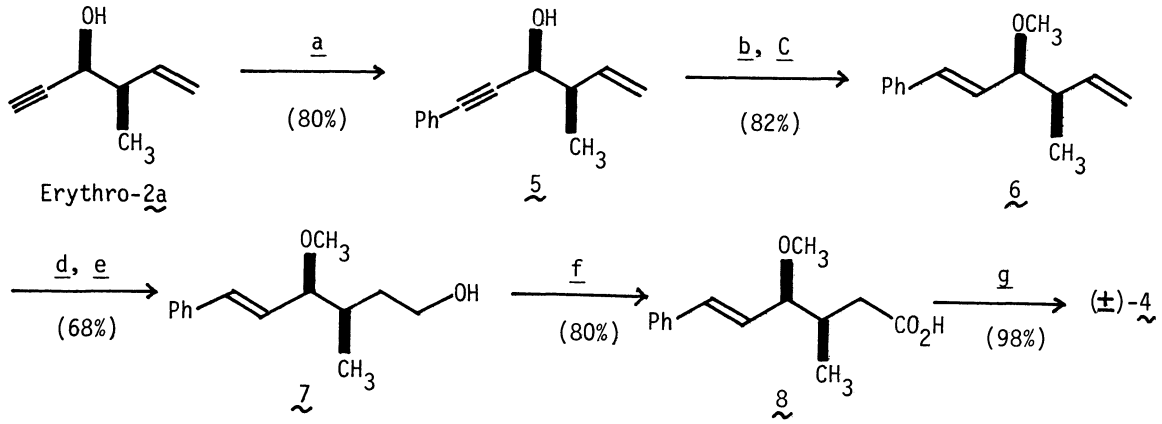
3



4

The propargylic alcohol 2a (98% erythro) obtained from (Z)-1b was first converted to 5[10] without appreciable epimerization[11] according to the phenylation procedure of Hagiwara.[12] Then, 5 was directly reduced to the (E)-cinnamylic alcohol[13] which was converted to the methyl ether (6).[14] Hydroboration of 6 with 9-BBN[15] followed by oxidation afforded the methoxy-alcohol 7.[16] Oxidation of 7 to acid 8 followed by esterification furnished the desired ester 4.[17] Sicne 4 has been elaborated to 3 in two simple steps,[8] the present synthesis of (±)-4 constitutes a new formal synthesis of (±)-oudemansin.

Scheme 1.



a PhI, $(Ph_3P)_2PdCl_2$/CuI, Et_2NH (under ultrasonic irradiation); b $LiAlH_4$, THF, refl.; c NaH/CH_3I, THF, refl.; d 9-BBN, THF, 0°C; e H_2O_2, aq. NaOH, 0°C; f O_2, Pt-C, aq. $NaHCO_3$, 90-100°C; g CH_2N_2, Et_2O.

This research was generously supported by the Kurata Foundation and the Grant-in-Aid for Special Project Research from Ministry of Education, Science and Culture, Japan.

References

1) Review on acyclic stereocontrol via sigmatropic rearrangements: T. Nakai, K. Mikami, and N. Sayo, *J. Synth. Org. Chem., Jpn.*, 41, 100 (1983).

2) a) T. Nakai, K. Mikami, S. Taya, and Y. Fujita, *J. Am. Chem. Soc.*, 103, 6492 (1981); b) T. Nakai, K. Mikami, S. Taya, Y. Kimura, and T. Mimura, *Tetrahedron Lett.*, 22, 69 (1981); c) K. Mikami, K. Fujimoto, and T. Nakai, *ibid.*, 24, 513 (1983); d) K. Mikami, K. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, 48, 279 (1983).

3) The geometric pair of 1b and 1c was prepared from 1a in 80 - 90% yields via treatment with EtMgBr followed by reaction with Me_3SiCl and CH_3I, respectively.

4) For the determination of erythro/threo ratio for 2a, see Ref. 2a.

5) 2c: bp 62-67°C/7 mmHg; GLC (PEG 20M, 120°C), t_R 48.0 min (erythro) and 54.0 min (threo). The stereochemical assignment was confirmed by GLC comparison of its hydrogenation product with an erythro-rich mixture obtained via reaction of 2-methylbutanal with n-PrMgBr; the authentic mixture: GLC (PEG 20M, 80°C), t_R 63.8 min (major) and 67.0 min (minor).

6) The effects are reasonably explicable in terms of our own transition-state model.[2d] A detailed discussion will be described in a full paper.

7) T. Anke, H. J. Hecht, G. Schramm, and W. Steglich, *J. Antibiot.*, 32, 1112 (1979).

8) T. Nakata, T. Kuwabara, Y. Tani, and T. Oishi, *Tetrahedron Lett.*, 23, 1015 (1982).

9) Throughout the sequence, the stereochemistry of each intermediate was confirmed through NMR comparison of the corresponding threo-rich sample independently prepared from threo-2a.

10) NMR ($CDCl_3$), δ 1.18 (d, J=6.9 Hz, CH_3), 4.47 (d, J=4.95 Hz, >CH-OH), 7.10-7.57 (m, 5H). The NMR spectrum of threo-5 shows a doublet at δ 4.43 (J=6.0 Hz) due to the carbinol proton.

11) A similar phenylation of the methyl ether of 2a led to considerable epimerization.

12) S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagiwara, *Synthesis*, 1980, 627.

13) Alternatively, this alcohol can be obtained directly via the [2,3]-Wittig process of (*Z*)-crotyl (*E*)-cinnamyl ether; unfortunately, the reaction was found to exhibit only 70% of erythro-selectivity.[2d] For the NMR data of the threo- and erythro-isomer, see ref 2d.

14) NMR (CCl_4), δ 1.05 (d, J=6.3 Hz, CH_3), 3.27 (s, OCH_3), 6.50 (d, J=15.0 Hz, PhCH=CH-).

15) An attempted hydroboration using BH_3 led to considerable epimerization and a lower yield.

16) Purification by preparative TLC (silica gel, ether/hexane (1 : 1)) gave 7 with 93% of erythro-purity; erythro-7: NMR (CCl_4), δ 0.93 (d, J=6.3 Hz, CH_3), 3.29 (s, OCH_3),6.07 (dd, J= 16.2 and 9.0 Hz, 1H), 6.50 (d, J=16.2 Hz, 1H); threo-7: δ 3.20 (s, OCH_3).

17) The spectral data (IR and NMR) of this product were in agreement with the values reported in ref 8 ; NMR (CCl_4), δ 1.00 (d, J=6.0 Hz, 3H), 1.90-2.63 (m, 3H), 3.31 (s, 3H), 3.64 (s, 3H), 3.53-3.77 (m, 1H), 6.05 (dd, J=15.6 and 6.6 Hz, 1H), 6.55 (d, J=15.6 Hz, 1H), 7.06-7.60 (m, 5H); IR (neat), 1735, 1085, 970, 750, 675 cm^{-1}.

(Received June 24, 1983)