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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

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The [2,3]-Wittig variant of (\underline{Z}) -crotyl ether involving trimethylsilylethynyl (or l-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 (\pm) -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.



While the rearrangement of (<u>E</u>)-crotyl propargyl ether (<u>la</u>, R = C≡CH) has been found to exhibit an extremely high (essentially 99%) threo-selectivity, the (<u>Z</u>)-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 <u>modified</u> 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 (<u>±</u>)-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 <u>la</u> could improve the diastereoselectivity. Thus, we carried out the rearrangement of geometric pairs of <u>lb</u> $(X = SiMe_2)^{3}$ and <u>lc</u> $(X = CH_2)^{3}$

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.

		<i>n</i> -BuLi, - THF/hexane	85°C	HO		^{CH} 3		ŀ	// Н	0	сн ₃	(2)	
(Z)- 0	or (E)-1			Erytł	nro-2	2				Thre	eo-2		
able 1. Entry		Substrate (geometric purity) ^{a)}		ity) ^{a)}	Erythro :				reo	b)	Yield	Yield/% ^{c)}	
	1 ^{d)}	(Z)-1a, X=H	(98%)		88	:	12	(90	:	10)	56		
	2 ^{d)}	(<i>E</i>)-]a	(93%)		7	:	93	(1	:	99)	61	(76)	
	3	(Z)-1b, X=S	iMe ₃ (93%)		98	:	2	(100	:	0)	74		
	4	(E)-1b	(93%)		75	:	25	(73	:	27)	72		
	5	(Z)-1c, X=C	H ₃ (98%)		98	:	2	(100	:	0)	55	(74)	
	6	(E)-lc	(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 erythroselection by the introduction of the silyl group (entry 3); surprisingly enough, the observed degree slightly exceeds the geometric purity of the substrate used. (2) (<u>E</u>)-<u>1b</u> exhibits the opposite sense of stereoselection to those of (<u>E</u>)-<u>1a</u> and -<u>1c</u>, though the level is not so high; this anomaly is apparently responsible for the exceedingly high erythro-selectivity described above. (3) (<u>Z</u>)- and (<u>E</u>)-<u>1c</u> 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 <u>added</u> 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⁾



The propargylic alcohol 2g (98% erythro) obtained from (\underline{Z})-1b was first converted to $\underline{5}^{10}$ without appreciable epimerization¹¹⁾ according to the phenylation procedure of Hagiwara.¹²⁾ Then, $\underline{5}$ was directly reduced to the (\underline{E})-cinnamylic alcohol¹³⁾ which was converted to the methyl ether ($\underline{6}$).¹⁴⁾ Hydroboration of $\underline{6}$ with 9-BBN¹⁵⁾ followed by oxidation afforded the methoxy-alcohol $\underline{7}$.¹⁶⁾ Oxidation of $\underline{7}$ to acid $\underline{8}$ followed by esterification furnished the desired ester $\underline{4}$.¹⁷⁾ Sicne $\underline{4}$ has been elaborated to $\underline{3}$ in two simple steps,⁸⁾ the present synthesis of (\pm)- $\underline{4}$ constitutes a new formal synthesis of (\pm)-oudemansin.

Scheme 1.



^a PhI, $(Ph_3P)_2PdCl_2/CuI$, Et_2NH (under ultrasonic irradiation); ^b LiAlH₄, THF, refl.; ^c NaH/CH₃I, THF, refl.; ^d 9-BBN, THF, 0°C; ^e H₂O₂, aq. NaOH, 0°C; ^f O₂, Pt-C, aq. NaHCO₃, 90-100°C; ^g CH₂N₂, Et_2O .

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 c) K. Mikami, K. Fujimoto, and T. Nakai, *ibid.*, <u>24</u>, 513 (1983); d) K. Mikami, K. Kimura, N. Kishi, and T. Nakai, J. Org. Chem., 48, 279 (1983).
- 3) The geometric pair of lb and lc was prepared from la in 80 90% yields via treatment with EtMgBr followed by reaction with Me₃SiCl and CH₃I, 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 <u>n</u>-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.^{2 d)} A detailed discussion will be described in a full paper.
- 7) T. Anke, H. J. Hecht, G. Schramm, and W. Steglich, J. Antibiot., <u>32</u>, 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 (CDCl₃), δ 1.18 (d, J=6.9 Hz, CH₃), 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 (CCl₄), δ 1.05 (d, J=6.3 Hz, CH₃), 3.27 (s, OCH₃), 6.50 (d, J=15.0 Hz, PhC<u>H</u>=CH-).
- 15) An attempted hydroboration using BH₃ led to considerable epimerization and a lower yield.
- 16) Purification by preparative TLC (silica gel, ether/hexane (1 : 1)) gave <u>7</u> with 93% of erythro-purity; erythro-<u>7</u>: NMR (CCl₄), δ 0.93 (d, J=6.3 Hz, CH₃), 3.29 (s, OCH₃),6.07 (dd, J= 16.2 and 9.0 Hz, 1H), 6.50 (d, J=16.2 Hz, 1H); threo-<u>7</u>: δ 3.20 (s, OCH₃).
- 17) The spectral data (IR and NMR) of this product were in agreement with the values reported in ref 8; NMR (CCl₄), 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

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