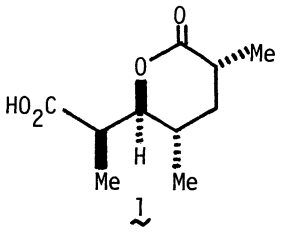
CHEMISTRY LETTERS, pp. 1725-1728, 1985.

[2,3]WITTIG REARRANGEMENT-BASED APPROACHES TO STEREOCONTROL OVER THREE CONTIGUOUS CHIRAL CENTERS. NEW ENTRIES TO THE (±)-PRELOG-DJERASSI LACTONE

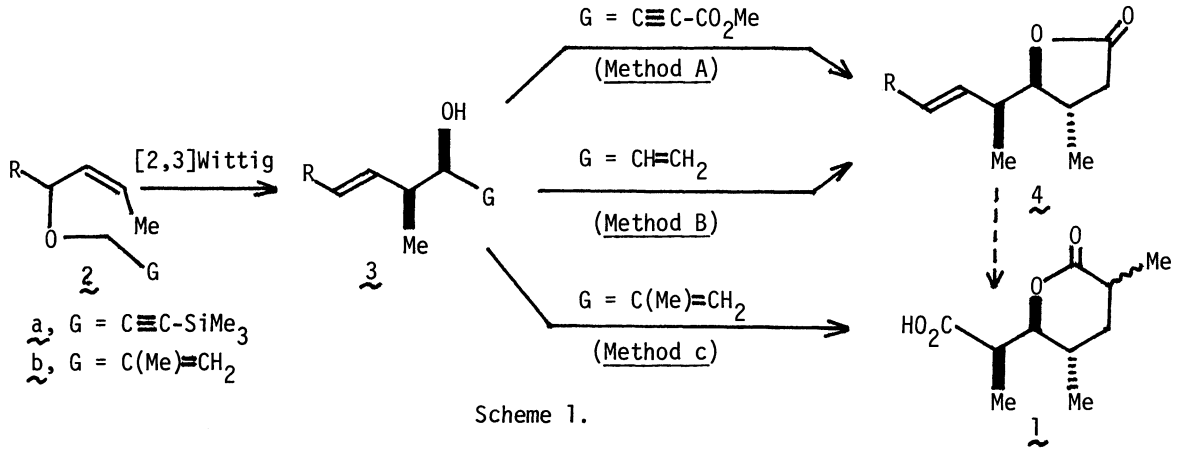
Ei-ichi NAKAI, Ei-ichiro KITAHARA, Noboru SAYO, Yoshio UENO,† and Takeshi NAKAI*
Department of Chemical Technology, Tokyo Institute of Technology,
Meguro-ku, Tokyo 152

Three [2,3]Wittig-based approaches for stereocontrol over three contiguous chiral centers are described within the synthesis of the title lactone. In these methods, the erythro-selective [2,3]Wittig variants are combined with one of the stereoselective processes: the Michael addition, the radical cyclization, and the hydroboration.

Considerable effort has currently been devoted to the development of methods for stereocontrol over three contiguous chiral centers, particularly for the synthesis of the Prelog-Djerassi lactone (1) and related lactones.[1] Since we developed highly diastereoselective [2,3]Wittig rearrangements,[2] our effort has recently been directed toward applications of the [2,3]Wittig strategy to stereocontrol over three contiguous chiral centers.[3] Our basic idea is to combine the highly diastereoselective [2,3]Wittig variants with stereoselective manipulations of the rearrangement products. We now report three distinct types of [2,3]Wittig-based approaches for stereocontrol over the three contiguous chiral centers within the context of the synthesis of (±)-1 and its potential precursor 4 (Scheme 1).[4]



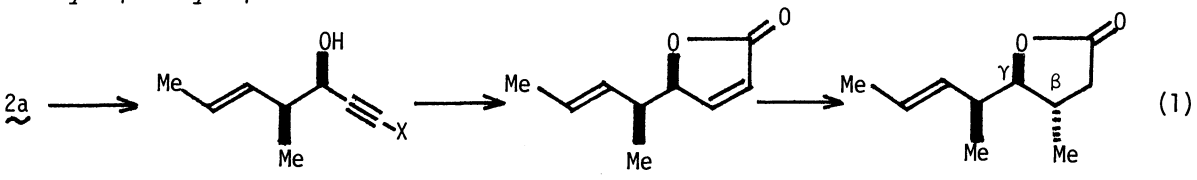
1



Scheme 1.

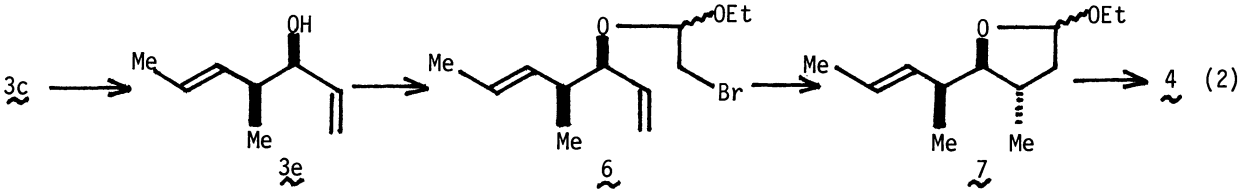
†Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Midori-ku, Yokohama 227; Deceased on February 27, 1985.

First, the synthetic sequence for method A is shown by Eq. 1, which involves the [2,3]Wittig rearrangement of 2a (R=Me)[2b] and the Michael addition to the butenolide 5 as the stereo-directing processes. Thus, the alcohol 3c (100% E and 98% erythro), prepared via the rearrangement of 2a followed by desilylation,[2b] was converted to the acetylenic ester 3d in 76% overall yield via the three conventional steps: silylation (t-$BuMe_2SiCl$, imidazole), treatment with methyl chloroformate (n-BuLi, THF), and hydrolysis (HCl, MeOH). Selective hydrogenation of 3d (Lindlar cat., MeOH) gave in 96% yield the butenolide 5[5] which was subjected to the Michael addition with lithium dimethyl cuprate (Et_2O, -78 °C) to afford in 85% yield the γ-lactone 4 as a single stereoisomer (by ^1H and ^{13}C NMR analysis).[6] The β,γ-trans(anti) configuration of 4 was assigned on the basis of the anti stereoselectivity reported for similar Michael additions to γ-alkyl butenolides[7] and confirmed through ^1H NMR comparison with the stereoisomers of closely related β-methyl-γ-alkyl-γ-lactones.[7]



3c, X=H; 3d, X=CO_2Me 5 4 (1)

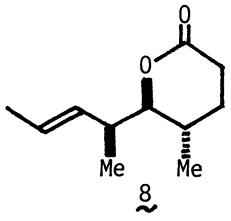
Second, the synthetic sequence for method B is depicted by Eq. 2, wherein the radical cyclization recently developed by one of the authors[8a] and Stork[8b] is employed as a stereo-directing process. The keys to this approach are, of course, the regio- and stereoselectivity of the radical cyclization of the acetal intermediate (6). In this specific case, the radical addition may take place onto the internal and/or the terminal double bond leading to the six- and/or five-membered product, respectively. Thus, the alcohol 3c described above was first converted, by selective hydrogenation, to the allylic alcohol 3e which was then subjected to the radical cyclization sequence according to the reported procedure.[8] Reaction of 3e with ethyl viny ether in the presence of N-bromosuccinimide afforded in 87% yield the acetal which was treated with tri-n-butyltin hydride (1.1 equiv.) in benzene at 60 °C in the presence of azobisisobutyronitrile (1.0 mol%) to afford in 87% yield the cyclized product 7 as a single regioisomer.[9] Finally, Jones oxidation of 7 gave in 82% yield the γ-lactone 4 as a single stereoisomer. The ^1H and ^{13}C NMR spectra of the product are in complete agreement with those of the lactone 4 obtained by method A, indicating that the regiospecific radical cyclization proceeds with an extremely high anti-selectivity as previously reported.[8]



3e 6 7 (2)

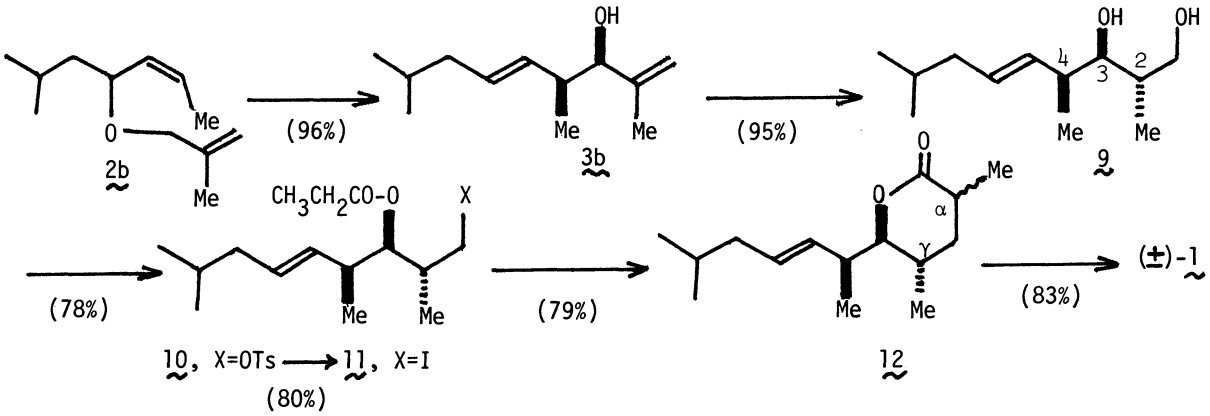
Particularly noteworthy at this stage is that the γ-lactone 4 obtained above could be converted, by the multi-step procedures recently developed for ring

enlargement of γ- to δ-lactones,[10] to the δ-lactone 8 that undoubtedly serves as a potential precursor of the Prelog-Djerassi lactone (1).[11]



8

Third, the synthetic sequence for method C is shown in Scheme 2, wherein the [2,3]Wittig process of 2b (R=$CH_2CH(CH_3)_2$) is combined with a hydroboration of the rearrangement product (3b).[4] Major problems in this approach are the chemo- and stereoselectivity in the hydroboration step. To solve the problems, we chose 9-borabicyclo[3.3.1]-nonane (9-BBN) in view of the high anti stereoselectivity reported for hydroborations of chiral methallylic alcohols with 9-BBN.[12] Thus, the rearrangement of 2b (>95% Z) was first carried out under the standard conditions,[2] to afford the alcohol 3b in >95% erythro-selectivity (by ^{13}C NMR assay).[13] The alcohol 3b was then treated with 9-BBN in THF at 0 °C to give, after usual oxidation, the diol 9 as an essentially single stereoisomer (by ^{13}C NMR analysis of its acetonide).[14] The 2,3-anti stereochemistry of 9 was assigned on the basis of Still's findings[12] and confirmed by the ^1H NMR spectrum of the acetonide.[14] Successive treatment of 9 with tosyl chloride and propanoic anhydride gave the tosylate 10[15] which was further treated with KI in acetone to afford the iodide (11).[15] The iodide was then reacted with LHDS (lithium hexamethyldisilylamide) in THF/HMPA (hexamethylphosphoramide) at -78 °C for 5 h to afford the δ-lactone (12).[15] Finally, oxidative cleavage of the double bond ($NaIO_4/RuCl_3$(cat.), aq. CH_3CN) gave the desired lactone 1 as a 57 : 43 mixture of the α-epimeric isomers (by the ^{13}C NMR spectrum[16] that is well correlated with the spectra reported for 1 and the α-epimer).[17] It should be noted here that the synthetic procedure for increasing the epimeric ratio and separating each epimer is now avaialble.[18]



Scheme 2.

References

1) Review: P. A. Bartlett, *Tetrahedron*, 36, 2 (1983). For more recent references, see: S. F. Martin and D. E. Guinn, *Tetrahedron Lett.*, 25, 5607 (1984).

2) a) T. Nakai, K. Mikami, S. Taya, and Y. Fujita, *J. Am. Chem. Soc.*, 103, 6492 (1981);b) K. Mikami, K. Azuma, and T. Nakai, *Tetrahedron*, 40, 2303 (1984).

3) For our previous work in this area, see: N. Sayo, E. Nakai, and T. Nakai, *Chem. Lett.*, in press.

4) After completion of this work, D. J.-S. Tsai and M. M. Midland [*J. Am. Chem. Soc.*, 107, 3915 (1985)] have reported the synthesis of the (+)-Prelog-Djerassi lactonic aldehyde based on a similar [2,3]Wittig-based strategy to method C reported herein. Their synthesis employs as the key steps the [2,3]Wittig process of an optically active substrate structually related to 2b and a stereoselective hydroboration (with dicyclohexylborane or 9-BBN).

5) ^{1}H NMR ($CDCl_3$, TMS), δ 1.17 (d, J=7.5 Hz, 3H), 1.73 (d, J=6.0 Hz, 3H), 2.53 (d,d, J=15.0 and 7.5 Hz, 1H), 5.07 (d,d,d, J=7.5, 2.3, and 1.2 Hz, 1H), 5.33-6.15 (m, 2H), 6.25 (d,d, J=7.5 and 2.3 Hz, 1H), 7.87 (d,d, J=7.5 and 1.2 Hz, 1H).

6) ^{1}H NMR ($CDCl_3$), δ 1.05 (d, J=7.2 Hz, 3H), 1.13 (d, J=6.0 Hz, 3H), 1.70 (d, J=5.7 Hz, 3H), 1.95-2.92 (m, 4H), 3.92 (d,d, J=7.5 and 6.0 Hz, 1H), 5.17-5.93 (m, 2H); ^{13}C NMR ($CDCl_3$), δ 16.3, 17.8, 19.3, 32.5, 36.9, 41.2, 90.5, 127.0, 131.2, 176.3.

7) J. P. Vigneron, R. Meric, and M. Dhaenens, *Tetrahedron Lett.*, 21, 2057 (1980); K. Tomioka, M. Tanaka, and K. Koga, *ibid.*, 23, 3401 (1982); Y. Yokoyama and M. Yunokihara, *Chem. Lett.*, 1983, 1245.

8) a) Y. Ueno, K. Chino, M. Watanabe, O. Moriya, and M. Okawara, *J. Am. Chem. Soc.*, 104, 5564 (1982);b) G. Stork, R. Mook, Jr., S. A. Biller, and S. D. Rychovsky, *ibid.*, 105, 3741 (1983).

9) ^{1}H NMR ($CDCl_3$), δ 1.03 (d, J=6.6 Hz, 3H), 1.06 (d, J=7.5 Hz, 3H), 1.18 (2t, J=3.0 Hz, 3H), 1.33-2.52 (m, 4H), 1.71 (d, J=4.5 Hz, 3H), 3.10-3.97 (m, 3H), 4.91 (d,d, J=7.5 and 6.0 Hz, 1H), 5.20-5.77 (m, 2H).

10) a) S. Takano, K. Morikawa, and S. Hatakeyama, *Tetrahedron Lett.*, 24, 401 (1983); b) K. Suzuki, K. Tomooka, T. Matsumoto, E. Katayama, and G. Tsuchihashi, *ibid.*, 26, 3711 (1985).

11) Actually, we attempted the conversion of 4 to 8 by applying Takano's five-step procedure (Ref. 10a), albeit in a low overall yield (ca. 30%) so far.

12) W. C. Still and J. C. Barrish, *J. Am. Chem. Soc.*, 105, 2487 (1983).

13) ^{13}C NMR ($CDCl_3$), δ 15.2, 18.2, 22.3, 28.6, 40.3(41.0), 42.1, 79.5(79.7), 119.9, 129.3, 133.2, 146.2. The peaks given in the parentheses are due to the threo-isomer of 3b (less than 3%).

14) ^{13}C NMR ($CDCl_3$), δ 12.9, 13.7, 19.2, 22.2, 28.5, 29.5, 31.5, 38.3, 42.0, 66.3, 88.5, 98.1, 127.9, 135.3; ^{1}H NMR ($CDCl_3$), δ 0.73 (d, J=7.2 Hz, 3H), 0.87 (d, J=6.6 Hz, 6H), 0.97 (d, J=6.6 Hz, 3H), 1.33 (s, 6H), 1.47-1.77 (m, 2H), 1.77-1.96 (m, 2H), 2.06-2.50 (m, 1H), 3.13-3.80 (m, $J_{2,3}$= ca. 10 Hz, 3H), 5.17-5.67 (m, 2H).

15) The ^{1}H NMR spectrum of this compound was in accord with the assigned structure.

16) ^{13}C NMR ($CDCl_3$), δ 8.15(8.89), 16.9(16.6), 17.2(17.4), 31.0, 36.4, 37.4, 41.2 (41.0), 83.0(86.5), 174.6(176.0), 177.5(177.3). The peaks given in the parentheses are due to the α-epimer of 1.

17) P. A. Bartlett and J. L. Adams, *J. Am. Chem. Soc.*, 102, 337 (1980); R. E. Ireland and J. P. Daub, *J. Org. Chem.*, 46, 479 (1981).

18) P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc.*, 101, 4779 (1979).

(Received August 27, 1985)