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APPLICATION OF ASYMMETRIC [2,3]WITTIG REARRANGEMENT TO STEREOCONTROL OVER THREE CONTIGUOUS CHIRAL CENTERS. A NEW SYNTHESIS OF (+)-BLASTMYCINONE

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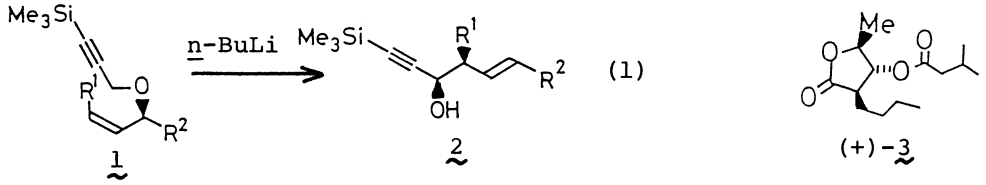
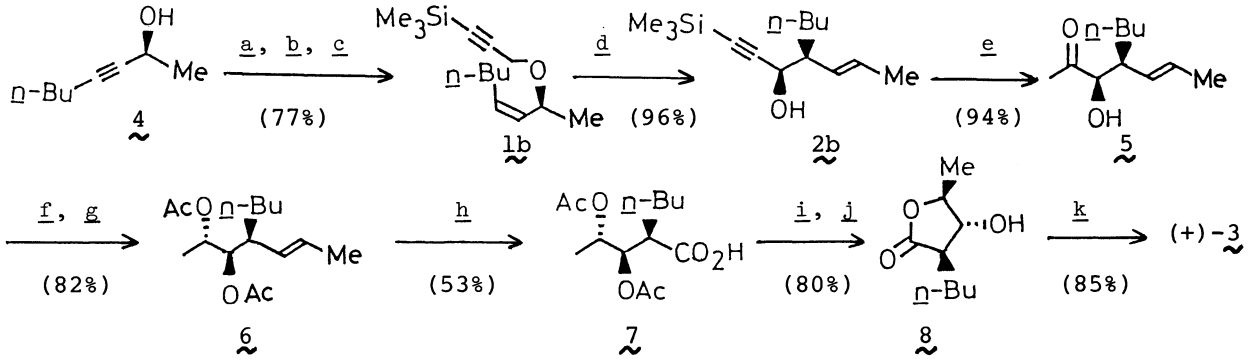
A new synthesis of (+)-blastmycinone is described which relies on the combination of the asymmetric [2,3]Wittig rearrangement with the selective reduction of an α-hydroxy ketone with zinc borohydride.

Recently we have reported that the [2,3]Wittig sigmatropic rearrangement of the enantiomerically-enriched (Z)-allylic ether 1a (R^1, R^2= Me) proceeds with complete chirality transfer and an extremely high syn-selectivity (Eq. 1).[1] We now report the first application of this type of asymmetric [2,3]Wittig variant to stereocontrol over three contiguous chiral centers within the context of the synthesis of (+)-blastmycinone (3),[2] a degradation product of the antibiotic antimycin A$_3$[3] (Scheme 1). This synthesis features the sequential combination of the asymmetric [2,3]Wittig process of 1b (R^1= n-Bu, R^2= Me) with the stereoselective reduction of the α-hydroxy ketone (5) with zinc borohydride.[4]



The requisite ether 1b was prepared from (S)-(-)-3-octyn-2-ol (4)[5] with 89% ee[6] via the conventional three-step sequence. The carbanion rearrangement of 1b was carried out under the standard conditions to afford the rearranged product (2b) in a high geometric (>98% E) and diastereomeric purity (>98% erythro).[7] The enantiomeric purity of 2b was 86% ee,[6] indicating that the sigmatropic shift proceeds with 97% chirality transfer. Usual hydration of 2b afforded the methyl ketone 5[8] which was then reduced with zinc borohydride according to Oishi's procedure[4,9] to give, after acetylation, the diacetate 6 in a high stereoselectivity (>98% 1,2-anti).[10] The oxidative cleavage of the double bond gave the acid 7 which was subjected to the hydrolysis-lactonization sequence to afford the lactone 8; mp 56.0-57.5 °C (lit[11] 49.5-50.5 °C). The spectral data (^{1}H and ^{13}C NMR, IR)[12] were in accord with the reported values.[2b,11] Finally, treatment of 8 with isovaleryl chloride gave (+)-blastmycinone (3) with 85% ee ($[\alpha]_D^{22}$ +9.4° (c 0.95, $CHCl_3$)), as judged from the highest literature value (+11.5°).[13] The ^{1}H NMR spectrum[14] was in agreement with the reported one.[11]



Scheme 1.

a:H_2/Lindlar cat., MeOH;b:HC≡C-CH_2Br/n-Bu_4NI/75% aq. NaOH;c:EtMgBr,THF ⟶ Me_3SiCl;d:n-BuLi, THF, -85 °C;e:H_2SO_4/$HgSO_4$(cat.), aq. THF; f: $Zn(BH_4)_2$, Et_2O, -10 °C;g:Ac_2O/pyridine, CH_2Cl_2;h:$RuCl_3 \cdot 3H_2O$/$NaIO_4$, aq. CH_3CN;i:K_2CO_3, aq. MeOH;j:conc. HCl;k:Isovaleryl chloride/pyridine

References

1) N. Sayo, K. Azuma, K. Mikami, and T. Nakai, *Tetrahedron Lett.*, 25, 565 (1984).
2) For the latest synthesis of (+)-3, see:a) T. Fujisawa, H. Kohama, K. Tajima, and T. Sato, *Tetrahedron Lett.*, 25, 5155 (1984);b) H. Uchiyama, Y. Kobayashi, and F. Sato, *Chem. Lett.*, 1985, 467;c) H. H. Wasserman and R. J. Gambale, *J. Am. Chem. Soc.*, 107, 1423 (1985).
3) M. Kinoshita, S. Aburaki, and S. Umezawa, *J. Antibiot.*, 25, 373 (1972).
4) T. Oishi and T. Nakata, *Acc. Chem. Res.*, 17, 338 (1984), and references therein.
5) Prepared from an optically-resolved (S)-1-butyn-3-ol via the standard method.
6) Determined by ^{19}F NMR analysis of the MTPA-ester (Mosher analysis): MTPA = (-)-α-methoxy-α-trifluoromethylphenylacetic acid.
7) The stereo-purity was determined by GLC (XE, 3 m, 190 °C) and ^{13}C NMR analysis.
8) After completion of this work, Fujisawa et al.[2a] reported the preparation of (-)-5 based on the ester enolate Claisen rearrangement of (R)-(E)-1-methyl-2-heptenyl glycolate and its converstion to (+)-3 via reduction with $Zn(BH_4)_2$[4] followed by a different sequence from that described herein.
9) T. Nakata, M. Fukui, and T. Oishi, *Tetrahedron Lett.*, 24, 2657 (1983).
10) The stereo-purity was determined by ^1H and ^{13}C NMR spectra and GLC (XE, 3 m, 190 °C): t_R = 24.5 min (anti) and 29.5 min (syn).
11) S. Aburaki, N. Konishi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 48, 1254 (1975).
12) IR (CCl_4), 3450 and 1760 cm^{-1};^1H NMR ($CDCl_3$, TMS), δ 0.96 (d, J=6.4 Hz, 3H), 1.32-2.20 (m, 6H), 1.45 (d, J=6.2 Hz, 3H), 2.50-3.10 (m, 2H), 3.83 (d, d, J= 7.0 and 9.0 Hz, 1H), and 4.21 (d, q, J=6.2 and 7.0 Hz, 1H);^{13}C NMR ($CDCl_3$), δ 177.5, 80.8, 78.6, 48.6, 28.2, 22.6, 18.2, and 13.8.
13) H. Yonehara and S. Takeuchi, *J. Antibiot., Ser. A*, 11, 254 (1958).
14) ^1H NMR ($CDCl_3$), δ 0.97 (d, J=6.5 Hz, 9H), 1.21-2.27 (m, 7H), 1.47 (d, J=6.5 Hz, 3H), 2.20 (s, 2H), 2.57-2.81 (m, 1H), 4.36 (d, d, J=4.7 and 6.5 Hz, 1H), and 4.97 (d, d, J=4.7 and 5.5 Hz, 1H).

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