HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF N-BOC DOLAISOLEUINE, UNUSUAL AMINO ACID IN DOLASTATIN 10

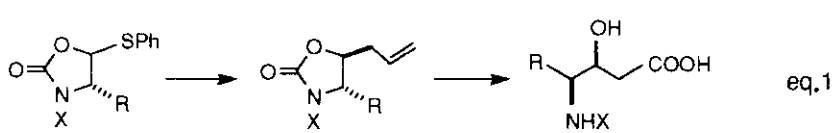
Shinzo Kano, Yoko Yuasa, and Shiroshi Shibuya*

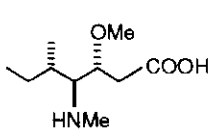
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract —— Photolysis of 5-phenylthiooxazolidin-2-one (**4**) in the presence of $(n\text{-}Bu_3Sn)_2$ and $n\text{-}Bu_3SnCH_2CH{=}CH_2$ afforded 5-allyl derivative (**5**) which was led to N-Boc dolaisoleuine (**11**), one component of dolastatine 10 (**2**), via **6-10**.

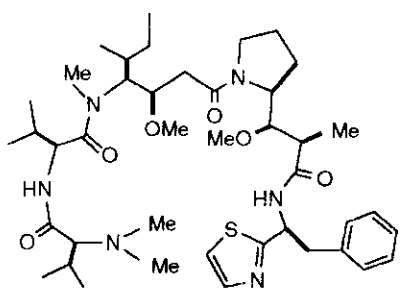
There are number of naturally occurring biologically active oligopeptides containing unusual β-hydroxy-γ-amino acids.[1-3] Diastereoselective synthesis of 2-amino alcohol continuously occupies a prime position in a synthesis of unusual amino acids containing it. Photo-initiated radical allylation of 5-phenylthiooxazolidin-2-ones, reported from our labolatory,[4] is a valuable tool for the preparation of 4,5-trans-5-allyloxazolidin-2-ones, which are useful intermediates for a synthesis of β-hydroxy-γ-amino acids (eq. 1).[4] By an application of this method, we examined the highly diastereoselective synthesis of dolaisoleuine (1),[3b] (3R,4S,5S)-4-methylamino-3-mehoxy-5-methylheptanoic acid, a component of dolastatin 10 (**2**),[3a] an antineoplastic peptide of marine origin, as shown in Scheme 1.

Scheme 1





1

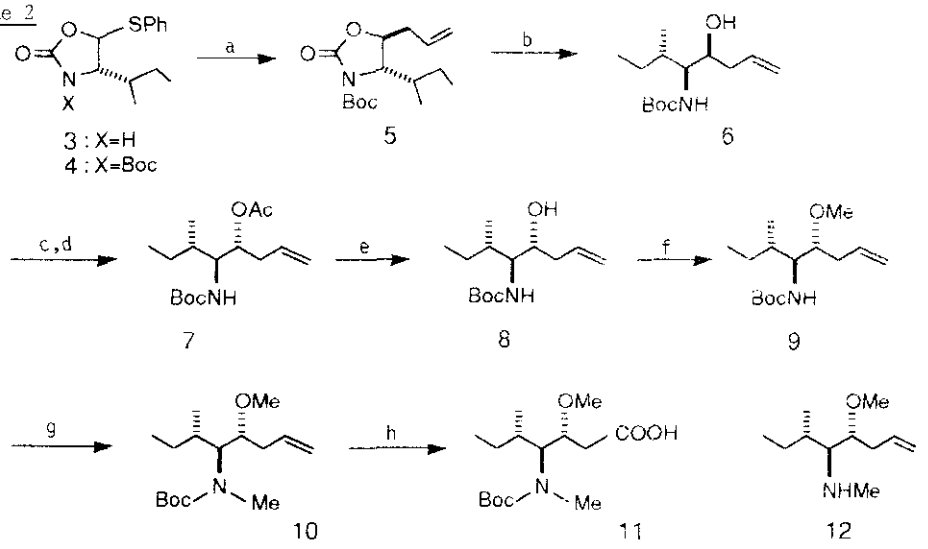


2

5-Phenylthiooxazolidin-2-one (**4**), obtained by t-butoxycarbonylation of **3** derived from (S)-isoleucine,[4] was irradiated with 500 W Hg lamp through pyrex filter (0.5 M solution in toluene/

acetonitrile (7:3)) in the presence of $(n\text{-}Bu_3Sn)_2$ (1 equiv.) and $n\text{-}Bu_3SnCH_2CH{=}CH_2$ (3 equiv.) to give **5**[5] in 80 % yield with high diastereoselectivity (4,5-trans/4,5-cis=100:0). Ring cleavage of 5 (MeOH, Cs_2CO_3) afforded the N-Boc 2-amino alcohol (**6**) in 78 % yield. Epimerization at 3-OH was successfully achieved as follows. Methanesulfonylation of **6**, followed by treatment with CsOAc (benzene, 18-crown-6, reflux)[6] and successive hydrolysis (K_2CO_3, MeOH, room temperature, 2 h) of the resulting acetate (**7**) gave **8**[5] in 68 % yield based on **6**. Selective O-methylation of **8** (MeI, TlOEt, DMF, room temperature, 2 h) yielded (**9**),[5] N-methylation of which (NaH, MeI, THF, room temperature, 3 h) afforded the desired N,O-dimethyl derivative (**10**) in 76 % yield. Its ^{1}H-nmr ($CDCl_3$) spectrum showed NCH_3 signal at δ 2.70 (br s) and OCH_3 signal at δ 3.37 (s). Interestingly, N-Boc N,O-dimethyl 2-amino alcohols such as **10**, **11**, **14**, **15**, **24** and **25** showed rather complicated signals in their ^{1}H-nmr spectra, though they were a single isomer. The signals due to NCH_3 appeared as a broad singlet or two singlets. This feature would be, most possibly, caused by rotaitional isomers.[7] In fact, ^{1}H-nmr ($CDCl_3$) spectrum of **12** obtained by removal of the Boc group on N showed sharp signals (δ 2.48, NCH_3; 3.35, $O\text{-}CH_3$). Oxidation of **10** ($RuCl_3$, $NaIO_4$) under the Sharpless conditions[8] yielded N-Boc dolaisoleuine (**11**)[5] in 67 % yield.

Scheme 2

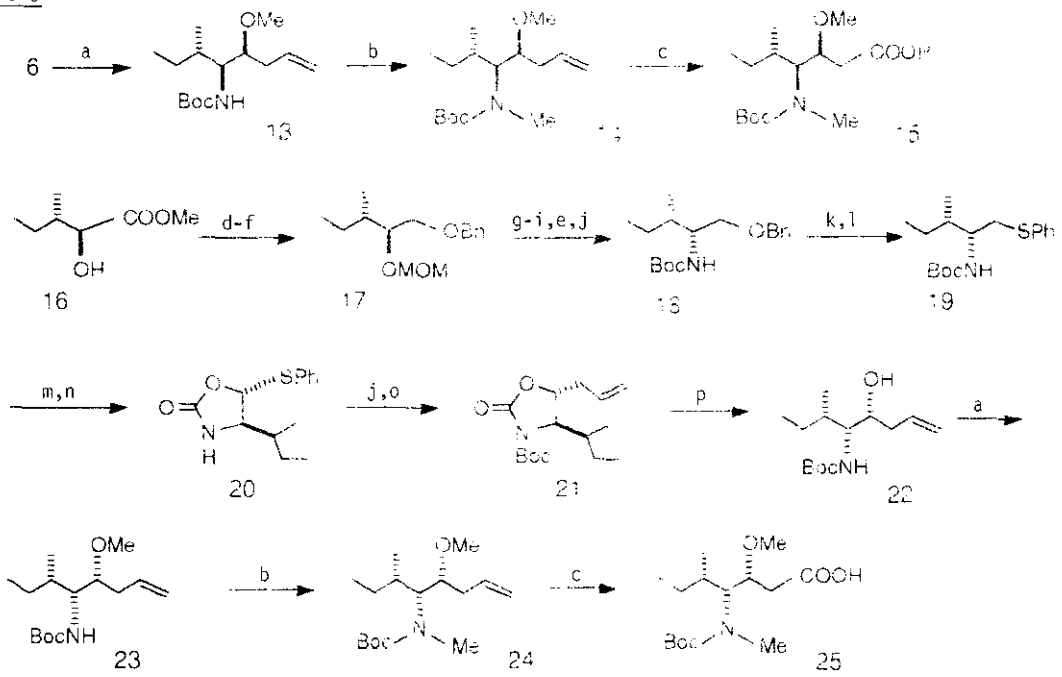


Reagents and Conditions: a. $(n\text{-}BuSn)_2/n\text{-}Bu_3SnCH_2CH{=}CH_2/h\nu$ 500 W Hg lamp, b. Cs_2CO_3/MeOH, c. $MeSO_2Cl/Et_3N/CH_2Cl_2$, d. CsOAc/18-crown-6/benzene/reflux 12 h, e. K_2CO_3/MeOH, f. TlOEt/ MeI/DMF, g. NaH/MeI/THF, h. $RuCl_3/NaIO_4/CCl_4$-MeCN-H_2O

Preparation of stereoisomers of dolaisoleuine would be significantly important from the point of view of the effect of chirality in the biological activity of dalastatin 10 possessing stereoisomer of dolaisoleuine. N-Boc (3S,4S,5S)-isomer (**15**) was easily prepared from **6** as depicted in the Scheme 3 according to the same manner as in the synthesis of **11**. N-Boc (3S,4S,5S)-isomer (**25**) was also

prepared from starting material easily available as follows. The sulfur containg N-Boc amine (**19**) derived from α-hydroxyester (**16**) by the usual way, was converted to 5-phenylthiooxazolidin-2-one (**20**). N-t-Butoxycarbonylation, followed by photo-radical allylation to afford **21**. Conversion of **21** to **25** was easily carried out according to the same method as above. The N-Boc dolaisoleuine and its stereoisomers would be useful for the synthesis of stereoisomers of dolastatin 10.

Scheme 3



Reagents and Conditions: a. $TlOEt$/ MeI/DMF, b. NaH/MeI/THF, c. $RuCl_3/NaIO_4$/ CCl_4-MeCN-H_2O, d. $MeOCH_2Cl$/i-$PrNEt_2/Ch_2Cl_2$, e. $LiAlH_4$/THF, f. NaH/$C_6H_5CH_2Br$/DMF, g. conc. HCl/THF-H_2O, h. $MeSO_2Cl/Et_3N/CH_2Cl_2$, i. NaN_3/DMF/90°C, j. Boc_2O/Et_3N/ DMAP/CH_2Cl_2, k. H_2/Pd-C/AcOH, l. $(PhS)_2$/n-Bu_3P/THF, m. NCS/CCl_4, n. $SnCl_4$/ CH_2Cl_2/-78°C-room temperature, 20 min, o. $(n\text{-}BuSn)_2$/n-$Bu_3SnCH_2CH{=}CH_2$/hν 500 W Hg lamp, p. Cs_2CO_3/MeOH,

REFERENCES AND NOTES

1. H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, H. Hamada, and T. Takeuchi, J. Antibiot., 1970, **23**, 259.

2. K. L. Rinehart, V. Kishore, S . Nagarajan, R. J. Lake, J. B. Gloer, F. A. Bozich, K.-M. Li, R. E. Maleczka, Jr., W. L. Todsen, M. H. G. Munro, D. W. Sullins, and R. Sakai, J. Am. Chem. Soc., 1987, **109**, 6846; Y. Hamada, Y. Kondo, M. Shibata, and T. Shioiri, J. Am. Chem. Soc., 1989, **111**, 669.

3. (a) G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer, and R. J. Bontems, J. Am. Chem. Soc., 1987, **109**, 6883; (b) G. R. Pettit, S. B. Singh, F. Hogan, P. L.-Williams, D. L. Herald, D. D. Burkett, and P. J. Clewlow,

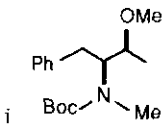
J. Am. Chem. Soc., 1989, 111, 5463.

4. S. Kano, T. Yokomatsu, and S. Shibuya, J. Org. Chem., 1989, **54**, 513. Recent publications on a preparation of 2-amino alcohls are cited therein.

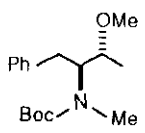
5. All new compounds gave satisfactory spectral data and microanalyses. All compounds were obtained as an oil except **4** and **8**. **4**: mp 79-80°C, Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.61; N, 3.92. **8**: mp 61-62°C, Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.22; H, 10.55; N, 5.40. Representative physical data of key compounds are as follows. ^{1}H-Nmr spectra were taken with Bruker AM-400 operating at 400 MHz and only characteristic signals are shown. **9**: ^{1}H-nmr ($CDCl_3$) δ 1.44 (9H, s, $C(CH_3)_3$), 3.35 (3H, s, OCH_3), **10**: ^{1}H-nmr ($CDCl_3$) δ 2.70 (3H, br s, NCH_3), 3.37 (3H, s, OCH_3); **11**: $[\alpha]_D$ -7.79° (c 0.02, methanol), ^{1}H-nmr ($CDCl_3$) δ 1.45 (4.5H, s, $C(CH_3)_3$), 1.46 (4.5H, s, 1/2x$C(CH_3)_3$), 2.70 (3H, br s, NCH_3), 3.41, 3.42 (each 1.5H, each s, OCH_3); **12**: ^{1}H-nmr ($CDCl_3$) δ 2.48 (3H, s, NCH_3), 3.35 (3H, s, OCH_3), ms m/z 185 (M^+); **13**: ^{1}H-nmr ($CDCl_3$) δ 1.44 (9H, s, $C(CH_3)_3$), 3.36 (3H, s, OCH_3); **14**: ^{1}H-nmr ($CDCl_3$) δ 1.44 (9H, s, $C(CH_3)_3$), 2.76, 2.79 (each 1.5H, each s, NCH_3), 3.35, 3.36 (each 1.5H, each s, OCH_3); **15**: ^{1}H-nmr ($CDCl_3$) δ 1.42 (3H, s, 1/3x$C(CH_3)_3$), 1.47 (6H, s, 2/3x$C(CH_3)_3$), 2.79 (3H, s, NCH_3), 3.35 (1H, s, 1/3xOCH_3), 3.36 (2H, s, 2/3xOCH_3); **23**: ^{1}H-nmr($CDCl_3$) δ 3.36 (3H, s, OCH_3); **24**: ^{1}H-nmr ($CDCl_3$) δ 2.76, 2.79 (each 1.5H, each s, N-CH_3), 3.34, 3.35 (each 1.5H, each s, OCH_3); **25**: $[\alpha]_D$ +19.00° (c 0.03, methanol), ^{1}H-nmr ($CDCl_3$) δ 1.42 (3H, s, 1/3x$C(CH_3)_3$), 1.46 (6H, s, 2/3x$C(CH_3)_3$), 2.79 (3H, s, NCH_3), 3.35 (1H, s, 1/3xOCH_3), 3.36 (2H, s, 2/3xOCH_3).

6. J. W. Huffman and R. C. Desai, Synthetic Commun., 1983, **13**, 553.

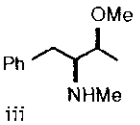
7. This interesting feature was usually observed in the N-Boc N-alkyl 2-amino alcohols such as **i** and **ii**. The ^{1}H-nmr spectra of **i** and **ii** showed rather complicated signals, though they are a single isomers. The characteristic signals in the ^{1}H-nmr spectra ($CDCl_3$, 400 MHz) of **i-iv** are as follows. **i**: δ 1.11, 1.14 (each 1.5H, d, J=6.3 Hz, CH_3), 1.30, 1.38 (each 4.5H, each s, $C(CH_3)_3$), 2.75, 2.83 (each 1.5H, each s, NCH_3), 3.28, 3.31 (each 1.5H. each s, OCH_3); **ii**: δ 1.14, (2H, d, J=6.2 Hz, 2/3xCH_3), 1.15 (1H, d, J=6.2 Hz, 1/3xCH_3), 1.33 (9H, s, $c(CH_3)_3$), 2.69 (3H, br s, NCH_3), 3.38 (1H, s, 1/3xOCH_3), 3.40 (2H, s, 2/3xOCH_3). **iii**: δ 1.22 (3H, d, J=6.3 Hz, CH_3), 2.60 (3H, s, NCH_3), 3.35 (3H, s, OCH_3). **iv**: δ 1.22 (3H, d, J=6.5 Hz, CH_3), 2.65 (3H, s, NCH_3), 3.26 (3H, s, OCH_3).



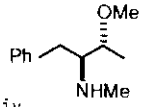
i



ii



iii



iv

8. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., 1981, **46**, 3936.

Received, 20th July, 1990