

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

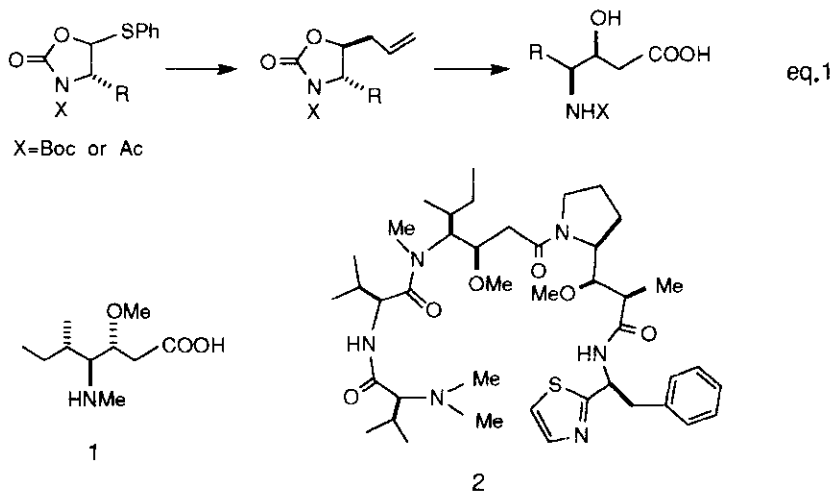
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Abstract — Photolysis of 5-phenylthioxazolidin-2-one (**4**) in the presence of $(n\text{-Bu}_3\text{Sn})_2$ and $n\text{-Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$ afforded 5-allyl derivative (**5**) which was led to N-Boc dolaisoleuine (**11**), one component of dolastatin 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-phenylthioxazolidin-2-ones, reported from our laboratory,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} (3*R*,4*S*,5*S*)-4-methylamino-3-methoxy-5-methylheptanoic acid, a component of dolastatin 10 (**2**),^{3a} an antineoplastic peptide of marine origin, as shown in Scheme 1.

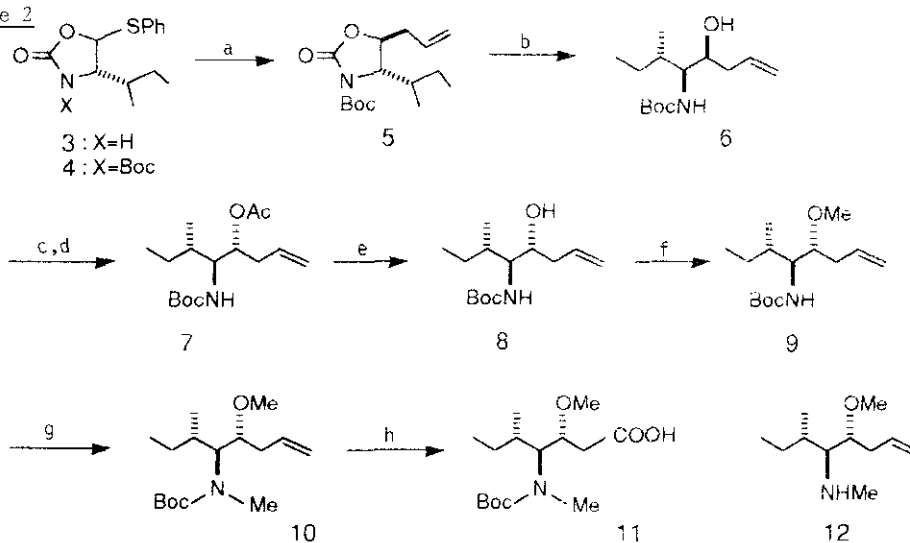
Scheme 1



5-Phenylthioxazolidin-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 $(n\text{-Bu}_3\text{Sn})_2$ (1 equiv.) and $n\text{-Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$ (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 $^1\text{H-nmr}$ (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 $^1\text{H-nmr}$ 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 rotational isomers.⁷ In fact, $^1\text{H-nmr}$ (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-CH_3). Oxidation of **10** (RuCl_3 , NaIO_4) under the Sharpless conditions⁸ yielded N-Boc dolaisoleuine (**11**)⁵ in 67 % yield.

Scheme 2

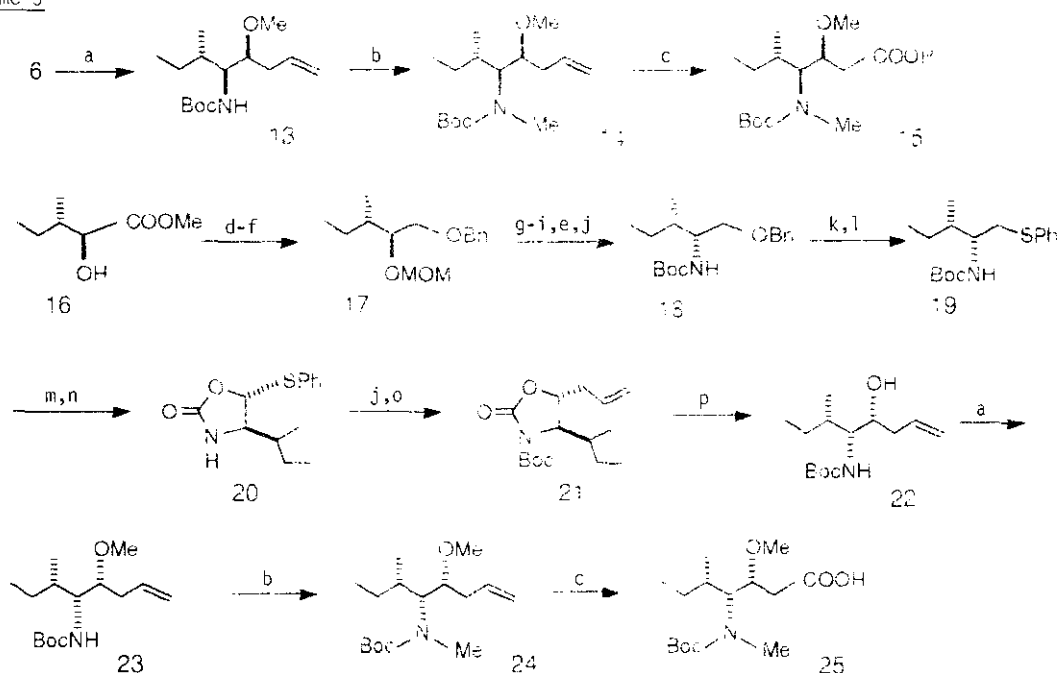


Reagents and Conditions: a. $(n\text{-Bu}_3\text{Sn})_2/n\text{-Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2/h\nu$ 500 W Hg lamp, b. $\text{Cs}_2\text{CO}_3/\text{MeOH}$, c. $\text{MeSO}_2\text{Cl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, d. $\text{CsOAc}/18\text{-crown-6}/\text{benzene}/\text{reflux}$ 12 h, e. $\text{K}_2\text{CO}_3/\text{MeOH}$, f. $\text{TlOEt}/\text{MeI}/\text{DMF}$, g. $\text{NaH}/\text{MeI}/\text{THF}$, h. $\text{RuCl}_3/\text{NaIO}_4/\text{CCl}_4\text{-MeCN-H}_2\text{O}$

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 containing 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 dolaisoleucine and its stereoisomers would be useful for the synthesis of stereoisomers of dolastatin 10.

Scheme 3



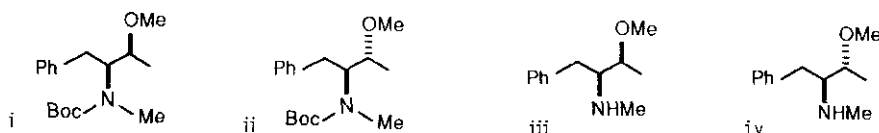
Reagents and Conditions: a. $\text{TiOEt} / \text{MeI} / \text{DMF}$, b. $\text{NaH} / \text{MeI} / \text{THF}$, c. $\text{RuCl}_3 / \text{NaIO}_4 / \text{CCl}_4 - \text{MeCN} - \text{H}_2\text{O}$, d. $\text{MeOCH}_2\text{Cl} / i\text{-PrNEt}_2 / \text{CH}_2\text{Cl}_2$, e. $1.1 \text{AlH}_4 / \text{THF}$, f. $\text{NaH} / \text{C}_6\text{H}_5\text{CH}_2\text{Br} / \text{DMF}$, g. conc. $\text{HCl} / \text{THF} - \text{H}_2\text{O}$, h. $\text{MeSO}_2\text{Cl} / \text{Et}_3\text{N} / \text{CH}_2\text{Cl}_2$, i. $\text{NaN}_3 / \text{DMF} / 90^\circ\text{C}$, j. $\text{Boc}_2\text{O} / \text{Et}_3\text{N} / \text{DMAP} / \text{CH}_2\text{Cl}_2$, k. $\text{H}_2 / \text{Pd} - \text{C} / \text{AcOH}$, l. $(\text{PhS})_2 / n\text{-Bu}_3\text{P} / \text{THF}$, m. $\text{NCS} / \text{CCl}_4$, n. $\text{SnCl}_4 / \text{CH}_2\text{Cl}_2 / -78^\circ\text{C} - \text{room temperature}, 20 \text{ min}$, o. $(n\text{-BuSn})_2 / n\text{-Bu}_3\text{SnCl}_2\text{CH}=\text{CH}_2 / \text{hv} 500 \text{ W Hg lamp}$, p. $\text{Cs}_2\text{CO}_3 / \text{MeOH}$.

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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. 1H -Nmr spectra were taken with Bruker AM-400 operating at 400 MHz and only characteristic signals are shown. **9**: 1H -nmr ($CDCl_3$) δ 1.44 (9H, s, $C(CH_3)_3$), 3.35 (3H, s, OCH_3), **10**: 1H -nmr ($CDCl_3$) δ 2.70 (3H, br s, NCH_3), 3.37 (3H, s, OCH_3); **11**: $[\alpha]_D -7.79^\circ$ (c 0.02, methanol), 1H -nmr ($CDCl_3$) δ 1.45 (4.5H, s, $C(CH_3)_3$), 1.46 (4.5H, s, $1/2 \times C(CH_3)_3$), 2.70 (3H, br s, NCH_3), 3.41, 3.42 (each 1.5H, each s, OCH_3); **12**: 1H -nmr ($CDCl_3$) δ 2.48 (3H, s, NCH_3), 3.35 (3H, s, OCH_3), ms m/z 185 (M^+); **13**: 1H -nmr ($CDCl_3$) δ 1.44 (9H, s, $C(CH_3)_3$), 3.36 (3H, s, OCH_3); **14**: 1H -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**: 1H -nmr ($CDCl_3$) δ 1.42 (3H, s, $1/3 \times C(CH_3)_3$), 1.47 (6H, s, $2/3 \times C(CH_3)_3$), 2.79 (3H, s, NCH_3), 3.35 (1H, s, $1/3 \times OCH_3$), 3.36 (2H, s, $2/3 \times OCH_3$); **23**: 1H -nmr ($CDCl_3$) δ 3.36 (3H, s, OCH_3); **24**: 1H -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**: $[\alpha]_D +19.00^\circ$ (c 0.03, methanol), 1H -nmr ($CDCl_3$) δ 1.42 (3H, s, $1/3 \times C(CH_3)_3$), 1.46 (6H, s, $2/3 \times C(CH_3)_3$), 2.79 (3H, s, NCH_3), 3.35 (1H, s, $1/3 \times OCH_3$), 3.36 (2H, s, $2/3 \times OCH_3$).
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 1H -nmr spectra of **i** and **ii** showed rather complicated signals, though they are a single isomers. The characteristic signals in the 1H -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, $2/3 \times CH_3$), 1.15 (1H, d, $J=6.2$ Hz, $1/3 \times CH_3$), 1.33 (9H, s, $c(CH_3)_3$), 2.69 (3H, br s, NCH_3), 3.38 (1H, s, $1/3 \times OCH_3$), 3.40 (2H, s, $2/3 \times OCH_3$). **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).



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Received, 20th July, 1990