THE DOLASTATINS 16. SYNTHESIS OF DOLAPHENINE[1§]

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Abstract - Synthesis of dolaphenine (2), the thiazole-containing unit of the strongly antineoplastic peptide dolastatin 10 (1), has been summarized. While conversion (4→7 or 4→11) of phenylalanine to thiazolidines (7) or thiazolines (11) was routinely uneventful, a dependable procedure for dehydrogenation of these intermediates to dolaphenine (2, Doe) proved elusive. While several types of specially prepared manganese dioxide were found most effective for the dehydrogenation, yields of dolaphenine varied from almost nil to over 70%. Some of these reactions resulted in partial to complete racemization of the phenylalanine derived chiral carbon.

The extraordinary potential of marine organisms as sources of completely new types of drugs for improving the treatment of cancer (and other serious diseases) provided the impetus for our initial[2] and continuing research in these vitally important areas. Current advances that illustrate marine animal constituents,[3-5] either now in human cancer clinical trial or soon to enter, include bryostatin 1,[6] didemnin B,[7] cephalostatins 1[8] and 7,[9] halichondrin B[10] and dolastatin 10 (1).[11] The clinical trial planned for dolastatin 10 required supply by a practical total synthesis and the present study was directed at obtaining the dolaphenine (2, Doe) unit. Subsequent contributions in this series describe useful syntheses of the other amino acid derived units and the final assembly of dolastatin 10.

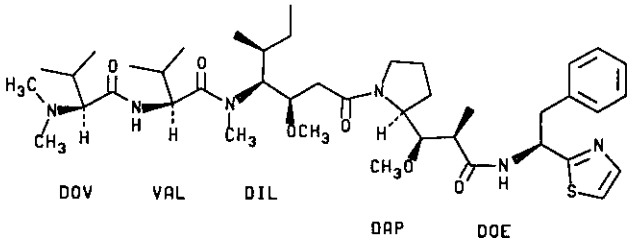
§ A contibution in commemoration of Dr. Arnold Brossi's 70th birthday

The thiazole ring has been commonly found in fungal metabolites and is a component of a variety of structurally diverse antibiotics which have been isolated from *Streptomyces* species.[12] More recently marine animal constituent investigations have resulted in discovery of a number of thiazole-containing and cytotoxic cyclic peptides.[11-13] The syntheses of several of these and isomers thereof, including dolastatin 3,[14-16] ascidiacyclamide,[17] patellamides A,[18] B[19,20] and C,[19] ulithiacyclamide[21,22] and ulicyclamide[23] have been accomplished. Each of these compounds contains a 2-(1-aminoalkyl)thiazole-4-carboxylic acid unit, the biosynthetic formation of which probably involves dehydrative cyclization of an amino acid-cysteinyl dipeptide. In this respect, dolastatin 10 (1) was found to be an exception as it was shown by extensive spectroscopic analyses[11] that the thiazole ring lacked substitution at both the 4- and 5-positions.

Thiazole-4-carboxylic acids have most often been prepared by the Hantzsch condensation. However, racemization usually occurs due to an acid catalyzed imine-enamine type tautomerization of the intermediate thiazoline.[24,25] When this investigation was first undertaken[25] a survey of the literature indicated that applications of the Hantzsch method either do not give the desired enantiomeric purity or involve a complex series of steps.[15,26,27]

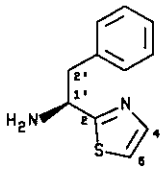
In 1984 Hamada and co-workers[16] described the syntheses without racemization of thiazole-4-carboxylic acid esters *via* the condensation of *S*-cysteine methyl ester (3a) with the *N*-protected α-amino aldehyde, similar in type to a synthesis carried out by Iwakawa *et al.*[28] This mimicry of the probable biosynthetic pathway for the formation of thiazole-4-carboxylates was appealing both in the directness of the route and in the retention of the optical activity.[29] Application of such a procedure to the synthesis of Doe (2) was studied in detail.

The Hamada[16,30] synthesis of β-amino alcohols proceeded by methylation of the *N*-protected acid followed by selective reduction of the ester with sodium borohydride and lithium chloride to give rise to the alcohol in good yield. Alternatively borane tetrahydrofuran can be used very efficiently for the direct, selective reduction of protected amino acids to the



DOLASTATIN 10

1



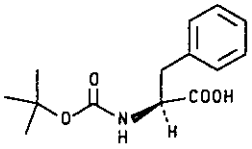
DOLAPHENINE (DOE)

2

3a, R = NH_2, R' = CO_2CH_3

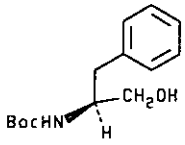
b, R = NH_2, R' = H

c, R = NH_3Cl, R' = H



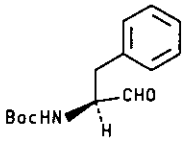
4

BH_3.THF



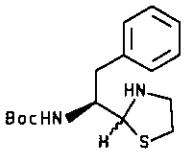
5

5 SO_3.pyridine, $(CH_3)_2SO$, $(C_2H_5)_3N$



6

3b or 3c + $(C_2H_5)_3N$, benzene



7

corresponding alcohols.[31-33] In our hands treatment of Boc-phenylalanine (4)[34] with this reagent gave rise to alcohol (5) in 90-96% yield. Oxidation[35] with dimethyl sulfoxide[36] derived reagents provides a versatile method for conversion of alcohols to aldehydes. Although a variety of activators have been used, the complex of sulfur trioxide with pyridine (the Parikh-Doering method)[37] has the advantage of room temperature operation without excessive yields of side products.[16,30,38-41] We found that treating Boc-phenylalaninol (5) with the sulfur trioxide-pyridine complex in dimethyl sulfoxide (containing triethylamine) produced aldehyde (6) in up to 94% yield.[42] The aldehyde could be stored at 0° for days at a time without loss of optical activity but was generally used immediately in the next reaction. Next Boc-phenylalaninal (6) was stirred in benzene with 2-aminoethanethiol (cysteamine; 3b) to give a diastereomeric mixture of the thiazolidines (7) in quantitative yield, or with the hydrochloride salt (3c) in the presence of triethylamine to give 7 in somewhat lower yield. At this point, only oxidation of the diastereomers (7) was required to give Boc-dolaphenine (8).

Manganese dioxide has been used extensively as a dehydrogenating agent.[43] For example,[44] 1,2-oxazoles were produced in quantitative yield from 4,5-dihydro-1,2-oxazoles when the substrate was treated with active γ-manganese dioxide in refluxing benzene (water being removed azeotropically). Barton[45] effectively dehydrogenated methyl 2-benzamidomethylthiazoline-4-carboxylate under mild conditions using manganese dioxide to give the thiazole carboxylate. The Hamada group[16] used activated manganese dioxide in syntheses of aminoalkylthiazole-4-carboxylic acid esters and later reported[41] that industrial chemical manganese dioxide gave better results (up to 69% yield).

We prepared activated manganese dioxide according to modifications[46] of the Attenburrow[47] procedure but only realized low yields (to 10%) of thiazole (8) using this oxidant. Activated manganese dioxide from Sigma-Aldrich Co. gave similarly disappointing results (*ca.* 5%). Battery grade manganese dioxide (type M) from Chemetals, Inc. gave somewhat better results with yields of 14% on average (and as much as 18%) and proved to be more consistent in its effect; it was noted, however, that use of battery grade manganese dioxide sometimes

gave rise to racemization, from 10 - 100% depending on the batch of oxidant. A side product produced in even lower yield (3%) was shown to be dihydrothiazole (9). Apparently the lack of a carboxylate substituent at the 4-position adversely affects the ease of dehydrogenation. Also this disadvantage is compounded by loss of material due to strong adsorption on the oxidant.[45] With the type M manganese dioxide the thiazolidine was treated in either of two ways. The oxidant (in up to 20- or 30-fold molar excess, depending on the scale) was added to a solution of the substrate, usually in benzene. The mixture was stirred with azeotropic removal of water. The use of dichloromethane as solvent and variation in temperature from 25°C to 55°C did not seem to affect the yield. In the second procedure a solution of the thiazolidine in dioxane was eluted through a column of manganese dioxide according to the Barton[45] method. Either procedure gave similarly low yields of thiazole.

While we evaluated active manganese dioxide prepared by a number of methods[43] along with products of various activities available from commercial sources, efforts were concentrated on the effectiveness of types produced by Chemetals, Inc. In Table 1 are presented the yields of thiazole (8) produced when these oxides were used on a small scale (*ca.* 50 mg substrate with 2 g manganese dioxide).

Yields varied depending on the type of oxidant and procedure used. In general yields were higher than those previously achieved, being almost 70% in one case. Results were not consistently reproducible, and it was found that yields dropped dramatically when the reaction was carried out on a larger scale (5-15g substrate), but overall the better procedures of Table 1 gave rise to useful amounts of thiazole. Alternative methods of oxidation were next investigated. The use of ferric chloride,[48] sulfur at temperatures of up to 190°C,[48] palladium trifluoroacetate with maleic acid,[49] Fremy's salt,[50] phenylselenenyl bromide,[51] potassium ferricyanide[52] and sulfuryl chloride[53] failed or gave other products. Because of partial success with manganese dioxide, other metal oxides were studied in the dehydrogenation reaction. Treatment with lead dioxide or selenium dioxide yielded aldehyde (6), as did oxidation with potassium persulfate. Molten sulfur[54] appeared by tlc to give traces of thiazole (8) when heating time was kept at a minimum. Palladium on carbon[55] in

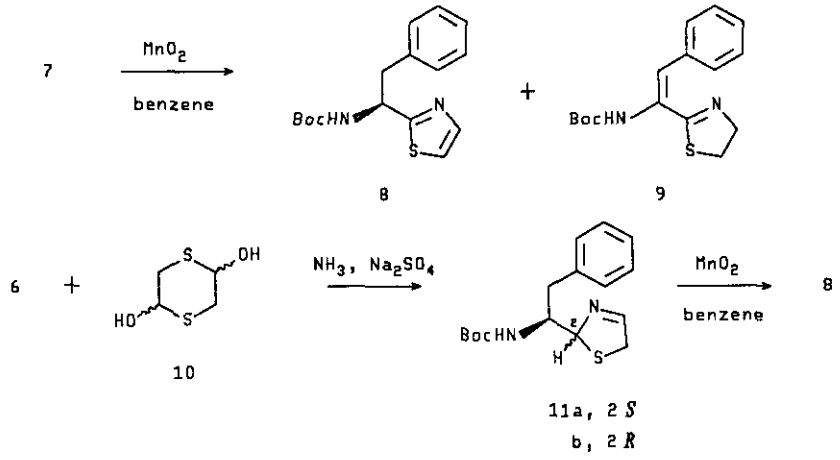


Table 1. Dehydrogenation of Thiazolidine 7 to Thiazole 8 Employing Manganese Dioxide

Type of MnO_2[a]	% yield Flask Method	Column Method
FarM™	11	17
		16.5
177-1	36	38
		38
		43.5
177-2	45	42
		42
		51
		41
HP (batch a)	52	30
	53	48
	66	49
(batch b)	0.0	0.0
(batch c)	10	
CIR	48	29
	52.5	41
	48	47

a, MnO_2 Type:	FarM™	177-1	177-2	HP	CIR
%Mn	60.0	59.5	61.5	62.9	61.5
$\%MnO_2$	90.0	89.9	92	99	92
BETSA (M^2/g)	110	54	40	1.4	35
Por.Vol.(cc/g)	.29	.12	.06	.002	.05
Avg.Por.Diam.(Å)	125	100	<20	200	<10
E° MnO_2/H^+ (Mv)	1275	1280	1325	1235	1320

refluxing *p*-cymene or in the presence of sulfur also appeared to cause oxidation to thiazole (**8**) but only in trace amounts (observed by tlc); similar results were obtained with phenanthrenequinone.[45] Of all the methods of dehydrogenation attempted with thiazolidine **7** only nickel peroxide[56] gave the *N*-protected dolaphenine (**8**) in detectable (7% yield) amounts. At this juncture other synthetic approaches to dolaphenine (**2**) were undertaken and the following method was found the best, albeit still lacking. Here Boc-phenylalaninal (**6**) was treated with 1,4-dithiane-2,5-diol (**10**) and ammonia to afford thiazoline (**11**) in 92% yield as a diastereomeric mixture. A sample of **11** was resolved for analytical purposes and the structures were confirmed by spectroscopic means. The ^{1}H nmr signals in the spectrum of **11a** (2*S*) were assigned using COSY.

The thiazoline mixture was treated with manganese dioxide (type M; Chemetals) in benzene by the first procedure described above for thiazolidine (**7**). On a small scale (~0.5 g) thiazole (**8**) was produced in 48% yield, but again yields dropped to about 14% when larger-scale reactions were performed. An investigation of alternative methods of oxidation offered no improvement. Again, a series of metal oxides were examined. Lead dioxide, molybdenum trioxide, iron (II, III) oxide, mercury (II) oxide and copper (II) oxide proved ineffective and selenium dioxide caused reversion to aldehyde (**6**). Sulfuryl chloride[53] in dichloromethane, palladium trifluoroacetate with maleic acid[49] in tetrahydrofuran or dimethoxyethane gave no product, nor did chloranil[57] in a variety of solvents. Treatment of thiazoline (**11**) with palladium on charcoal in refluxing *p*-cymene for 30 min gave thiazole (**8**) in 60% yield. With longer reaction times the product was destroyed and overall this route proved impractical. At present manganese dioxide appears the best reagent for converting thiazolidine (**7**) and thiazoline (**11**) to Boc-dolaphenine (**8**). Recent reports by Japanese groups[58-61] concerning the synthesis of dolastatin 10 (**1**) have described the preparation of Doe (**2**) employing oxidation of thiazolidine (**7**) by manganese dioxide[59-61] with yields similar to our experience or by way of forming the thiazole in 56% enantiomeric excess from Boc-phenylalanine[58,59,61] according to Schmidt's[27] modification of the Hantzsch method. The last of these[61] also describes a more efficient synthesis: asymmetric reduction of the carbonyl

group in benzyl 2-thiazolyl ketone (formed almost quantitatively from phenylacetic acid) is followed by a modified Mitsunobo reaction and yields Boc-Doe (8) in 52.5% overall yield. Efforts to find a more efficient synthesis of dolastatin 10 (1) through a high-yielding preparation of Doe (2) have very recently been advanced by Bredenkamp.[25] The application of their modification of the Hantzsch reaction has resulted in excellent yields (96%) of optically pure Boc-Doe (8).[25b]

Thiazole (8) was originally characterized by spectroscopic analysis. The ^{1}H nmr spectrum displayed the diagnostic doublets typical of the H-4 and H-5 positions.[62] As described in our earlier communication[63] and in greater detail in the sequel, thiazole (2) was stored as the Boc-derivative (8) until coupled with dolaproine (Dap). Coupling of the resulting amide with the required tripeptide as previously outlined[63] gave a peptide identical with natural dolastatin 10 (1), thus proving that the phenylalanine derived thiazole unit of the natural product has the *S* configuration.

EXPERIMENTAL

Battery grade manganese dioxide and other grades (see Table 1) were supplied by Chemetals, Maryland. All other reagents were obtained from Sigma-Aldrich Chemical Co. Solvents were redistilled; tetrahydrofuran was distilled from lithium aluminum hydride prior to use. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. Evaporation of solvents was performed under reduced pressure. Analtech silica gel GF and GHLF plates were used for thin layer chromatography (tlc) and developed with 3% ceric sulfate in 3N sulfuric acid spray. Column chromatography was performed on E. Merck (Darmstadt) silica gel (Kieselgel 60, <0.063 and 0.063-0.200 mm for gravity column and 0.040-0.063 mm for flash column). Melting points are uncorrected and were determined on a Kofler-type hot stage apparatus. Optical rotation measurements were recorded using a Perkin-Elmer 241 polarimeter. Infrared measurements were conducted with a Nicolett MX-1 FT spectrophotometer or on a Mattson 2020 Galaxy series FT-IR spectrophotometer equipped with CompuAdd. Nuclear magnetic resonance spectra were recorded in deuteriochloroform with tetramethylsilane as internal

reference using Bruker AM 400 (^{13}C) and Varian Gemini 300 MHz (^{1}H unless specified otherwise) instruments and chemical shifts are recorded in ppm (δ). The EIMS mass spectra were measured with a Finnigan-MAT 312 instrument and the SP-SIMS (FAB) mass spectra were recorded with a Kratos MS 50 instrument in the NSF regional mass spectrometry facility at the University of Nebraska. Elemental analyses were determined by Dr. A. W. Spang (Spang Microanalytical Laboratory, Eagle Harbor, MI).

***N*-(*tert*-Butoxycarbonyl)-L-phenylalanine (4).** To a stirred, cooled (0°C) solution of L-phenylalanine (16.69 g, 101.03 mmol) in dioxane (40 ml), water (20 ml) and aqueous sodium hydroxide (1*N*, 125 ml) was added di-*tert*-butyl dicarbonate (97%, 25 g, 111.12 mmol). The mixture was stirred at 0°-25°C for 2 h and was then recooled to 0° before acidification to pH 3 with 10% aqueous citric acid solution. Extraction with ethyl acetate (3 x 300 ml) followed by washing of the organic layer with water (2 x 300 ml) and removal of the solvent *in vacuo* yielded 4 (26.26 g, 99 mmol, 98%) as an oil which became crystalline on standing and was recrystallized from hexane, mp 87-88°C [lit.,[65] mp 84-85°C].

***N*-(*tert*-Butoxycarbonyl)-L-phenylalaninol (5).** A solution of 4 (26.26 g, 99 mmol) in tetrahydrofuran (50 ml) was cooled to 0° and stirred under argon before the slow (over 30 min) addition of borane-tetrahydrofuran complex (1 M, 200 mmol). The mixture was stirred for 1.5 h at 0°C to room temperature and was then poured with care onto ice-water (200 ml) and, with the addition of water (300 ml), was partitioned between the aqueous phase and ether (3 x 300 ml). The ethereal layers were washed with water (2 x 300 ml). Removal of the solvent *in vacuo* yielded 5 as a crystalline solid (22.80 g, 91.7%) which recrystallized from hexane-ether in needles, mp 93-94°C [lit.,[33d] mp 93-95°C], $[\alpha]_D$-28.0° (c 2.7, $CHCl_3$) [lit.,[33d] $[\alpha]_D$ -26.0° (c 1.1, $CHCl_3$)], R_f 0.2 [hexane-ethyl acetate (2:1)].

***N*-(*tert*-Butoxycarbonyl)-L-phenylalaninal (6).** To a solution of 5 (24.0g, 95.5 mmol) in anhydrous dimethyl sulfoxide (100 ml) which was being stirred under argon at 15°C was added freshly distilled (over calcium hydride) triethylamine (46.3 ml, 332 mmol). Sulfur trioxide-pyridine complex (52.8 g, 332 mmol) was then added slowly (four batches over 40 min) and the resulting reddish-brown solution was stirred at 10-15°C for 90 min before being poured onto

ice-water (150 ml) to quench the reaction. The aqueous mixture was extracted with ethyl acetate (4 x 60 ml) and the combined organic layers were then washed sequentially with 10% citric acid solution (2 x 50 ml), water (1 x 50 ml), saturated sodium bicarbonate solution (2 x 50ml) and brine (1 x 50 ml). Removal of the solvent *in vacuo* yielded **6** as a crystalline solid (22.43 g, 90 mmol, 94.2%), mp 69-70°C. In another experiment the reaction was carried out as above except that the sulfur trioxide-pyridine complex was added quickly in one portion. Reaction did not go to completion even with prolonged stirring and the product was collected as a powder from hexane ether in a lower yield (76.9%), mp 67-69°C, $[\alpha]_{589}$ -37.5°, $[\alpha]_{578}$ -38.6, $[\alpha]_{546}$ -44.0, $[\alpha]_{436}$ -76.4, $[\alpha]_{365}$ -73.7 (c, 1.0, $CHCl_3$) [lit.,[35] $[\alpha]_D$ +2.9° (c 3.0, CH_2Cl_2)], R_f 0.36 [hexane-ethyl acetate (3:1)].

***N*-(*tert*-Butoxycarbonyl)-*S*-tetrahydrodolaphenine (7).** **Method A**: A solution of **6** (4.3 g, 17.3 mmol) and 2-aminoethanethiol (**3b**, 1.6 ml, 20.7 mmol) in anhydrous benzene (50 ml) was stirred under argon at room temperature for 4 h. Removal of the solvent followed by quick filtration of the residue through a pad of silica gel [vacuum column; eluant: hexane-ethyl acetate (1:1)] yielded **7** as a solid which crystallized from hexane-acetone (5.2 g, 98%), mp 73-74°C, $[\alpha]_D$ 0.0° (c 1, MeOH), R_f 0.16, 0.10 [hexane-ethyl acetate (2:1)]. Ir (NaCl) 3309, 3304, 2975, 1709, 1496, 1454, 1366, 1247, 1168 cm^{-1}. ^1H Nmr (400 MHz) δ ($CDCl_3$) 7.31-7.20 (5H, m, aromatic), 4.98 (1H, d, J = 9.6 Hz, NH), 4.51 (1H, br s, NH), 4.39 (1H, m, CH), 3.58 (1H, m), 2.95 (2H, m), 2.81 (2H, m), 2.68 (2H, m), 1.40, 1.38 (9H, s). HRFABms m/z 315.1717 [$(M+Li)^+$, calcd for $C_{16}H_{24}N_2O_2SLi$; 315.1719]. Anal. Calcd for $C_{16}H_{24}N_2O_2S$: C, 62.31, H, 7.84, N, 9.08. Found: C, 62.62, H, 7.90, N, 9.31.

Method B: To a solution of **6** (7.63 g, 30.605 mmol) in benzene (100 ml) was added triethylamine (99%; 6.7 ml, 47.59 mmol) and 2-aminoethanethiol hydrochloride (**3c**; 5.4 g, 47.53 mmol). The mixture was stirred under argon at room temperature for 4 h. Removal of the solvent followed by purification of the residue on a silica gel flash column [eluant: hexane-ethyl acetate (9:1→1:1)] yielded **7** which crystallized from hexane/acetone in clusters (7.3 g, 23.735 mmol, 77.5%).

***N*-(*tert*-Butoxycarbonyl)-*S*-dolaphenine (8).** **Method A:** To a suspension of battery grade (Type M) manganese dioxide (14 g) in anhydrous benzene was added a solution of **7** (2 g, 6.5 mmol) in benzene (50 ml) and the mixture was stirred under argon at 55°C for 24 h. A further aliquot of oxidant (7 g) was added and stirring was continued for 48 h. The mixture was filtered through a narrow bed of silica gel, the solids being washed sequentially with benzene (200 ml), ethyl acetate (1000 ml), chloroform (200 ml) and chloroform-acetone (1:1; 200 ml). Removal of solvent *in vacuo* from the combined filtrate yielded a residue which was purified by flash column chromatography [200 x 30 mm, eluant: hexane-ethyl acetate (19:1)] to yield thiazole (**8**) (0.25 g, 13%) as an amorphous solid which crystallized from ethyl acetate-hexane in granules, mp 106-107°C, $[\alpha]^{30}_{D}$ -23.3° (c 0.6, $CHCl_3$), R_f 0.21 [hexane-ethyl acetate (5:1)]. Ir (NaCl) 3290, 2977, 1700, 1517, 1498, 1454, 1440, 1392, 1367, 1249, 1168, 698 cm^{-1}. ^1H Nmr (400 MHz) δ ($CDCl_3$) 7.75 (1H, d, J = 3.2 Hz, H-4), 7.25 (1H, d, J = 3.2 Hz, H-5), 7.19-7.25 (3H, m, Ph), 7.08 (2H, m, Ph), 5.28 (2H, m, H-1', NH), 3.29 (2H, d, J = 6.4 Hz, H-2'), 1.40 (9H, s, $C(CH_3)_3$). ^{13}C Nmr δ ($CDCl_3$) 170.39 (C-2), 159.28 (C-4), 155.43 (CO), 137.28 (*ipso*-Ph), 129.39 (*o*-Ph), 128.56 (*m*-Ph), 127.12 (*p*-Ph), 113.93 (C-5), 80.04 ($\underline{C}(CH_3)_3$), 55.37 (C-1'), 39.25 (C-2'), 28.04 ($C(\underline{C}H_3)_3$). HRFABms m/z 311.1411 [$(M+Li)^+$, calcd for $C_{16}H_{20}N_2O_2SLi$: 311.1406]. Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13, H, 6.62, N, 9.20. Found: C, 63.14, H, 6.62, N, 9.23.

Continued elution of the flash column afforded dihydrothiazole **9** (53 mg, 3%), mp 98-100°C, R_f 0.15 [hexane-ethyl acetate (5:1)]. Ir (NaCl) 3400, 2977, 1714, 1583, 1482, 1449, 1367, 1337, 1244, 1160, 772 cm^{-1}. ^1H Nmr (400 MHz) δ ($CDCl_3$) 7.23-7.50 (5H, m, Ph), 6.71 (1H, s, H-2'), 6.65 (1H, br s, NH), 4.37 (2H, t, J = 8 Hz, H-4), 3.38 (2H, t, J = 8 Hz, H-5), 1.34 (9H, s, $C(CH_3)_3$). HRFABms m/z 311.1396 [$(M+Li)^+$, calcd for $C_{16}H_{20}N_2O_2SLi$: 311.1406]. Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13, H, 6.62, N, 9.20. Found: C, 63.09, H, 6.67, N, 9.07.

Method B: The activated manganese dioxide (6 g) was mixed with dry dioxane and the slurry was added to a dry glass column (7.5 mm internal diameter). The column was lightly packed by eluting with dioxane under a positive pressure of nitrogen. A solution of thiazolidine **7** (0.20 g) in dry dioxane (4 ml) was allowed to flow through the column over a 4 h contact

period. Following the removal of an initial fraction containing side products, thiazole **8** was eluted in average yields of 14%.

Method C: A solution of the thiazolidines (**7**, 51.9 mg, 0.17 mmol) in anhydrous dioxane (5 ml) was stirred vigorously under argon. To the solution was added MnO_2 (type HP, 2.00 g, 23 mmol) and the mixture was stirred for 3 h. It was then filtered through celite and removal of solvent yielded a red oil which was purified by column chromatography [silica gel, eluant: hexane-ethyl acetate (5:1)]. The isolated yield of pure *N*-Boc-dolaphenine was 64% and that based on recovered starting material was 77%.

Method D: To a solution of **6** (24.1 g, 96.7 mmol) in ether (200 ml) was added 1,4-dithiane-2,5-diol (**10**, 15.3 g, 97%, 97.5 mmol) and anhydrous sodium sulfate (10 g). Ammonia (gas) was bubbled through the reaction mixture at room temperature for 2 h after which the salt was filtered off and the solvent was removed *in vacuo*. The residue was purified on a silica gel (0.0063-0.200 mm) column (6 x 52 cm) [eluant: hexane-toluene-acetone (3:2:2)] to yield a mixture of the 2,5-dihydrothiazoles (**11**, 27.39 g, 92.4%) which could be used without further purification in the next reaction. An aliquot of the diastereomers (188 mg) was resolved by gravity column chromatography [silica gel 0.040-0.063 mm, 2.5 x 112 cm, eluant: hexane-toluene-acetone (3:2:2)] to yield **2(*S*)-[1'(*S*)-*N*-(*tert*-butoxycarbonyl)amino-2'-phenyl]ethyl-2,5-dihydro-1,3-thiazole** (**11a**, 90 mg) as an oil, $[\alpha]_D$ -16.6° (c, 0.1, $CHCl_3$), R_f 0.54 [hexane-toluene-acetone (3:2:2)]. Ir (KBr) 3339, 2976, 2930, 1701, 1497, 1248, 1167, 735 cm^{-1}. ^1H Nmr δ ($CDCl_3$) 7.45 (1H, m, H-4), 7.25-7.15 (5H, m, Ph), 5.73 (1H, m, H-2), 4.80 (1H, d, J = 9.4 Hz, NH), 4.45 (1H, m, H-1'), 3.87-3.85 (2H, m, H-5), 2.80-2.60 (2H, m, H-2'), 1.32 (9H, s, $C(CH_3)_3$). ^{13}C Nmr δ ($CDCl_3$) 161.19 (C-4), 155.45 (CO), 137.48 (*ipso*-Ph), 129.41 (*o*-Ph), 128.62 (*m*-Ph), 126.67 (*p*-Ph), 87.00 (C-2), 79.23 ($\underline{C}(CH_3)_3$), 54.96 (C-1'), 43.86 (C-5), 39.26 (C-2'), 28.01 ($C(\underline{C}H_3)_3$). EIms m/z (relative intensity) 306 (M^+, 0.08%), 220 (16.31%), 164 (23.10%), 120 (51.81%), 91 (28.13%), 86 (15.66%), 84 (14.05%), 59 (10.08%), 57 (100%). Continued elution yielded **2(*R*)-[1'(*S*)-*N*-(*tert*-butoxycarbonyl)amino-2'-phenyl]ethyl-2,5-dihydro-1,3-thiazole** (**11b**, 98 mg) as a crystalline solid, mp 112.0-112.7°C, $[\alpha]_D$ +16.1° (c, 0.1, $CHCl_3$), R_f 0.50 [hexane-toluene-acetone (3:2:2)]. Ir (KBr) 3378, 2982, 2932, 1688, 1508,

1258, 1169, 745. ^{1}H Nmr δ ($CDCl_3$) 7.56 (1H, m, C-4), 7.30-7.16 (5H, m, Ph), 5.80 (1H, m, H-2), 4.37 (1H, d, J = 9.6 Hz, NH), 4.25 (1H, m, H-1'), 3.92-3.88 (2H, m, H-5), 2.93-2.77 (2H, m, H-2'), 1.31 (9H, s, $C(CH_3)_3$). ^{13}C Nmr δ ($CDCl_3$) 162.57 (C-4), 155.7 (CO), 137.89 (*iso*-Ph), 129.56 (*o*-Ph), 128.61 (*m*-Ph), 126.62 (*p*-Ph), 86.25 (C-2), 79.39 ($\underline{C}(CH_3)_3$), 55.75 (C-1'), 44.32 (C-5), 37.85 (C-2'), 28.05 ($C(\underline{C}H_3)_3$). EIms m/z (relative intensity) 306 (M^+, 0.19%), 220 (13.14%), 164 (20.47%), 120 (57.23%), 91 (18,34%), 87 (10.14%), 86 (15.29%), 69 (9.94%), 57 (100%). Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.71, H, 7.24, N, 9.14. Found: C, 62.43, H, 7.45, N, 9.02.

To a solution of the thiazolines (**11**, 520 mg, 1.7 mmol) in dry benzene (20 ml) was added manganese dioxide (1 g; type M). The suspension was heated under reflux for 1 h and a further aliquot of oxidant was then added. Heating under reflux was continued for 1 h before the solids were removed by filtration. The solvent was removed *in vacuo* and purification of the residue by column chromatography [silica gel 0.063-0.200 mm, 1.8 x 59 cm, eluant: hexane-acetone (4:1)] yielded ***N*-Boc-dolaphenine** (**8**, 0.19 g, 36.8%) and starting material (0.12 g). (The yield of product based on recovered starting material was 47.8%.)

In another experiment, a suspension of manganese dioxide (500 g, type M) in benzene (600 ml) was warmed on a Büchi rotary evaporator at 40°C until 100 ml of solvent, including water (1-2 ml), was lost by distillation. A solution of **11** (48.0 g, 156.65 mmol) in benzene (300 ml) was added to the suspension. An exothermic reaction took place and the mixture was cooled and stirred on the rotary evaporator at 40°C for 4 h with the loss by distillation of another aliquot of benzene (100 ml). The oxidant was then removed by filtration, the solids being washed with toluene (1000 ml). The solvent was removed *in vacuo* from the filtrate and the dark red residue was purified by repeated flash chromatography [silica gel 0.040-0.063, 5.5 x 48 cm, eluant: hexane-toluene-methanol-2-propanol (15:3:1:1) followed by silica gel 0.040-0.063, 5.5 x 48 cm, eluant: ether-hexane-toluene (5:2:2)] to afford crude product (8.6 g). This red material was triturated with hexane-ethyl acetate (15:1) to give pure crystals of ***N*-Boc-*S*-dolaphenine** (**8**, 2.2 g). Removal of the solvent *in vacuo* from the filtrate followed by purification of the residue in two batches by flash column chromatography [silica

gel 0.040-0.063, 3.5 x 20 cm, eluant: hexane-ethyl acetate (15:1)] yielded a further aliquot (4.33 g) of ***N*-Boc-*S*-dolaphenine** (**8**, 6.53 g in total, 21.45 mmol, 13.7%), mp 106-107°C, $[\alpha]_D$ -23.3° (c 0.6, $CHCl_3$).

Method E: A Summary of the Treatment of Thiazolidine (7) with a Variety of Other Oxidizing Agents. **NiO_2**: Nickel peroxide (1.03 g) was added to a solution of **7** (87.5 mg, 0.28 mmol) in benzene (50 ml) and the mixture was heated under reflux for 60 h. Following filtration through celite, washing of the solids with ethyl acetate (200 ml) and removal of the solvent *in vacuo*, fractionation of the residue by column chromatography [eluant: hexane-ethyl acetate (9:1)] yielded 5.8 mg of **8** (0.02 mmol, 7%) and a mixture (64.9 mg) containing a trace of **8**. **Phenanthrenequinone**: A solution of **7** (9.21 mg; 0.03 mmol), phenanthrenequinone (17.5 mg, 0.084 mmol) and a catalytic amount of phenanthrenequinol in 15 ml of chloroform or benzene was heated under reflux for 1 - 60 h to yield only decomposition products. The use of dioxane or tetrahydrofuran as solvent gave thiazole (**8**) in 5% and 4% yields respectively. **S**: The solvent was removed from a suspension of sulfur (56 mg) in a solution of **7** (50 mg) in acetone (10 ml) and the dry mixture was heated in Wood's alloy (*ca.* 280°C) under argon for 1 min to give traces of thiazole. With longer heating times only decomposition occurred. At lower temperatures (to 140°C) no charring took place but no trace of desired product was apparent by tlc. **Pd/C (a)**: Palladium on carbon (10%, 1.0 g) was added to a solution of **7** (1.5 g) in *p*-cymene (30 ml) and the mixture was heated under reflux for 6 h. Filtration followed by removal of solvent under high vacuum yielded only traces of thiazole **8** . **Pd/C (b)**: A mixture of **7** (30 mg) and palladium on carbon (10%; 30 mg), dry or in naphthalene, xylene or cyclohexene, was heated at 220°C for 30 sec - 10 min to yield only decomposition products. In combination with sulfur (30 mg), without solvent, reaction of the above gave traces of **8**. **PbO_2**: Lead dioxide (2 g; 8.36 mmol) was added to a solution of **7** (500 mg; 1.62 mmol) in dry benzene (20 ml) and the mixture was stirred under argon at 50°C for 24 h. Isolation yielded aldehyde **6** (^1H, ^{13}C nmr). **SeO_2**: Selenium dioxide (2 g; 18.02 mmol) was added to a solution of **7** (500 mg; 1.62 mmol) in dry benzene (20 ml) and the mixture was stirred under argon at 50°C for 24 h. Isolation afforded aldehyde **6** (^1H, ^{13}C nmr). **$K_2S_2O_8$**: Potassium

persulfate (2 g; 7.40 mmol) in water (2 ml) was added to a solution of **7** (500 mg; 1.62 mmol) in dry benzene (20 ml) and the mixture was stirred under argon at 50°C for 24 h. The product was aldehyde **6** (^1H, ^{13}C nmr). **Chloranil**: A solution of **7** (0.1 g; 0.32 mmol) and chloranil (0.18 g; 0.73 mmol) in dry benzene (7 ml) was heated at 90°C under argon for 6 h to yield only decomposition products. **$Pd(OCOCF_3)_2$**: Treatment of **7** (102.6 mg; 0.33 mmol) with palladium trifluoroacetate (14.1 mg; 0.04 mmol) and maleic acid (134.8 mg; 1.16 mmol) in refluxing acetone (25 ml) appeared to give decomposition products. **SO_2Cl_2**: Treatment of **7** (56 mg; 0.18 mmol) with sulfuryl chloride (0.04 ml; 0.49 mmol) in dichloromethane (15 ml) at room temperature appeared to give decomposition products. **PhSeBr**: Reaction of **7** (103.7 mg; 0.34 mmol) with phenylselenenyl bromide (125.5 mg; 0.53 mmol) and lithium diisopropylamide (0.56 mmol) in tetrahydrofuran (12 mL) at -78° - -30°C gave a mixture of compounds which did not appear to include **8**. **$FeCl_3$**: Treatment of **7** (100 mg; 0.32 mmol) in ethanol (20 ml) with ferric chloride (350 mg; 1.73 mmol) at room temperature or 68°C for up to 64 h yielded a mixture of compounds which did not include **8**. When sodium acetate was used as buffer no reaction occurred. ***$K_3Fe(CN)_6$***: *Treatment of* **7** *(100 mg; 0.32 mmol) with potassium ferricyanide* (766.7 mg; 2.33 mmol) in aqueous sodium hydroxide (1*N*, 3.0 ml) and methanol (10 ml) yielded only baseline material by tlc. **Fremy's salt**: No reaction took place when **7** (52 mg; 0.17 mmol) was treated with Fremy's salt (300-700 mg; 1.12-2.61 mmol) and sodium carbonate (4%; 30 ml) in ethanol or glyme at room temperature under argon.

Method F: Reaction of Thiazoline 11 with Other Oxidizing Agents. Pd/C: Palladium on carbon (10%, 1.0 g) was added to a solution of **11** (0.5 g) in *p*-cymene (20 ml) and the mixture was heated under reflux for 30 min. Following filtration and removal of solvent under high vacuum, the residue was chromatographed [silica, 1.8 x 60 cm, eluant: hexane-acetone (4:1)] to yield **8** (0.15 g, 30%) and starting material (**11**, 0.35 g). When the reaction was repeated as above but heating was continued for 5 h, purification yielded **8** in 15% yield and with longer heating (6 h) no product was recovered. **S**: Treatment with sulfur at various temperatures appeared by tlc to give traces of product. **SeO_2**: Selenium dioxide (300 mg; 2.70 mmol) was added to a solution of **11** (100 mg; 0.33 mmol) in dry benzene (10 ml) and the

mixture was heated under reflux to yield aldehyde **6**. **PbO_2, MoO_3, Fe_3O_4, HgO, CuO in benzene; CuO in xylene; SO_2Cl_2 in dichloromethane; Pd/C in tetrahydrofuran; $Pd(OCOCF_3)_2$ with maleic acid in tetrahydrofuran or dimethoxyethane; chloranil in a variety of solvents.** The treatment of thiazoline (**11**) (100 mg) by heating under reflux with any of the preceeding reagents gave no trace of thiazole (**8**).

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