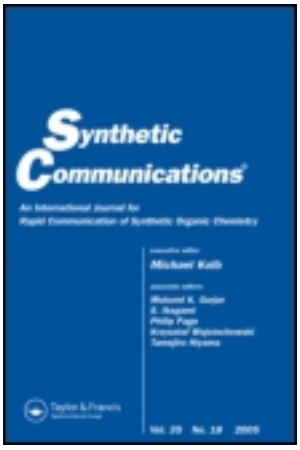

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Synthesis of 2-Amino-octa-4,7-Dien-1-ol (2): Key Intermediate for Mycothiazole Natural Product and Analogs

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Abstract: Starting from L-aminoacids, facile methods for the preparation 2-aminocta-4,7-dien-ol with different stereochemistry have been developed as key intermediates of mycothiazole and analogs.

Keywords: 1,2-Aminoalcohols, L-aminoacids, porcine kidney acetylase, Wittig reaction

Compounds containing 1,2-aminoalcohols are of great interest because of either their intrinsic properties or for their as powerful synthetic intermediates. This particular function is present in many drugs and in serine protease inhibitors.[1] Moreover, 1,2-aminoalcohols are useful as chiral ligands for catalysts[2] or as chiral auxiliaries in asymmetric synthesis.[3] These types of molecules have been employed to construct β-hydroxy amides and thioamides as key intermediates in the synthesis of thiazolines and oxazolines.[4]

Many bioactive natural products and analogs to natural products have been synthesized using cyclodehydration reactions of β-hydroxy amides or thioamides such as trunkamide,[5a] mollamide,[5b] hennoxazole,[6] *Lissoclinum* cyclopeptide alkaloids and analogs,[7] and curacin A analogs.[8]

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The marine natural product mycothiazole (**1**, Figure 1) exhibited anthelmintic activity[9] *in vitro* and selective toxicity toward lung cancer cells in the NCI in vitro 60-cell line panel. Results of the National Cancer Institute Human Tumor Cell Line Screen can be obtained at http://dtp.nci.nih.gov/, NSC 647640.

As part of our work in the search for bioactive compound analogs to marine natural products, we are interested in the synthesis of 1,2-aminoalcohols, intermediates for thiazolines/thiazoles and oxazolines/oxazoles analogs of mycothiazole.[10]

In the total synthesis of mycothiazole, Sugiyama and coworkers constructed the C_{18}-C_{14} diene fragment by two successive Stille couplings using a bromide-containing thiazol intermediate.[11]

Our planned synthesis of **1** and its derivatives is based on a convergent approach that combines aminoalcohols and acids, as shown in Scheme 1.

In this article, we describe our study on the synthesis of aminoalcohols of type **2**, key intermediates of **1** (C_{11}-C_{18} fragment) and reduced analogs thereof.

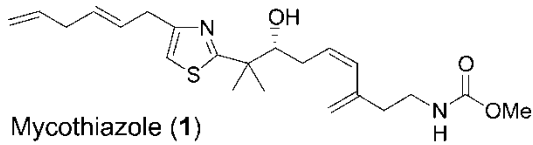
RESULTS AND DISCUSSION

Aminoalcohols of type **2**, with various stereochemistries, were synthesized using two methodologies: via Wittig reaction or by traditional aminoacid synthesis. First we investigated the Wittig reaction between the homologated Garner's aldehyde **7**,[12] and the nonstabilized ylide obtained from the Wittig salt **8**, (Scheme 2).

The aldehyde **7** was synthesized as shown in Scheme 2, starting from the oxazoline **3**.[12] Reduction of the ester function using $NaBH_4$/MeOH gave the alcohol **4**.[13] The best yield to perform the conversion of compound **5** to the cyanide **6** was obtained using the mesyl oxazolidine **5c**. Reduction of compound **6** by DIBALH allowed us to obtain the homologated Garner's aldehyde (**7**).

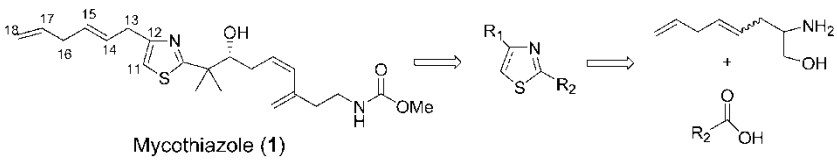
Wittig coupling of compound **7** and homoallylthriphenylphosphonium bromide (**8**) gave the protected aminoalcohols **9**. These products were obtained in variable yield and stereoselectivity depending on the experimental conditions, as shown in Table 1.

The *Z* alkene was the major product under Boden conditions (method A) as expected for a nonstabilized ylide.[14] Attempts to isomerize this *Z* alkene to



Mycothiazole (**1**)

Figure 1.



Scheme 1.

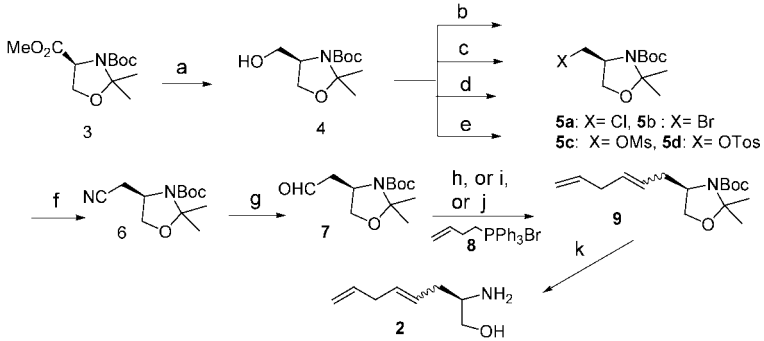
the *E* isomer (present in the natural product) using the conditions reported by matikainen and coworkers (method B) failed.[15] Nevertheless, the *E* alkene could be obtained using Schlosser modification of the Wittig reaction.[16] In this case, the product was obtained with the highest selectivity but the lowest yield (20%).

Protecting groups of compound **9** were removed by treatment with HCl 10% and MeOH at 40°C to give the *Z* or *E* isomer of (*R*) 2-aminocta-4,7-dien-ol (**2**) in 90% yield.

To improve both yield and stereoselectivity, an alternative route was investigated (Scheme 3).

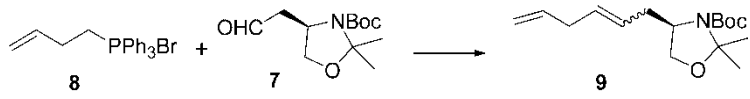
The synthesis involved the alkylation of acetamidemalonic ester (**11**) with alkenyl bromide **10**.

Compound **10** was synthesized using Normant methodology, starting from allylbromide and propargyl alcohol by a C-C coupling reaction.[17] DMPU was used as solvent instead of HMPA. The selective reduction of the alkynyl alcohol to the *E* double bound using $LiAlH_4$ and a subsequent substitution of the alcohol by a bromide allowed us to obtain the desired product **10** in 65% overall yield.



Scheme 2. a) $NaBH_4$, MeOH, rt, 12 h, 90% yield: b) CCl_4, PPh_3, benzene, reflux, 2 h, 61% yield; c) CBr_4, CH_2Cl_2, 0°C to rt, 63% yield; d) MsCl, Py, 0 to 40°C, 4 h, 90% yield; e) TosylCl, Py, 0°C, 48 h, 50% yield; f) NaCN, DMF, 90°C, 10 h, 70% yield; g) DIBALH, CH_2Cl_2, − 40°C to rt, 4 h, 70% yield; h) K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 4 h, 90% yield; i) K_2CO_3, hν, sodium/thioglycolate, dioxane/H_2O, 60% yield; j) PhLi, *t*BuOK, − 78 to − 30°C, THF, 20% yield: k) MeOH, HCl 10%, 40°C, 90% yield.

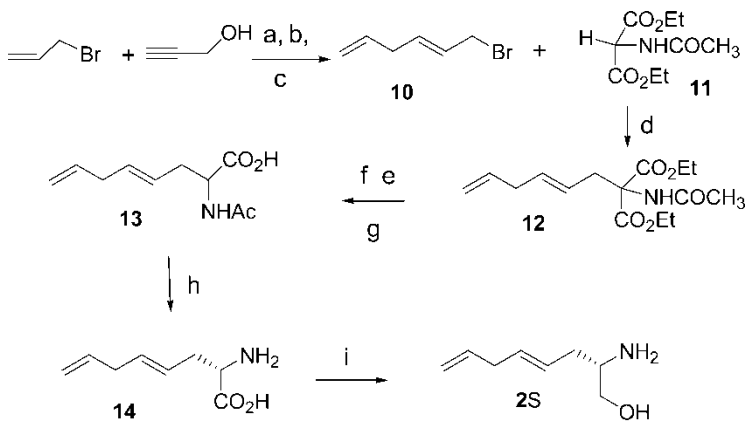
Table 1. Synthesis of compound **9** using different conditions



	Experimental conditions	Time and T (°C)	Solvent and T (°C)	Z/E[a]	Yield (%)
A	K_2CO_3 (1.5 eq.), 18-crown-6	4 h, reflux	CH_2Cl_2	90:10	90
B	K_2CO_3 (1.5 eq.), sodium thioglycolate	20 h, reflux	Dioxane/H_2O	75:25	60
C	PhLi (2 eq), *t*BuOH-*t*BuOK	2 h, −78 to −30	THF	13:87	20

[a]The Z/E ratio was determined by NMR spectroscopy on the crude reaction mixture.

The alkylation reaction of compound **11** proceeded with good yields, giving the ester **12**. To perform the decarboxylation, product **12** was first saponificated at room temperature with NaOH and the solution then acidificated with HCl to pH 2. Finally the diacidic aduct was isolated to perform decarboxylation reaction in refluxing H_2O/MeOH. Other decarboxylation media led to decomposition products. (*S*)-Aminoacid **14** was obtained in excellent yield from **13** by stereoespecific hydrolysis of the acetamide group with porcine kidney acetylase (EC 3.5.1.14).[17] Attempts to perform the hydrolysis



Scheme 3. Cu_2Cl_2, K_2CO_3, K_2CO_3, Na_2SO_3, DMPU, reflux, 5 h, 0% yield; b) $LiAlH_4$, THF, reflux, 2 h, 80%; c) CBr_4, Ph_3, CH_2Cl_2, 10°C, 2 h, 70% yield; d) EtONa, EtOH, 5 h, 80% yield; e) NaOH, rt, 24 h; f) HCl pH = 2; g) H_2O/MeOH, reflux, 6 h, 80% yield (e,f,g); h) Acylasa I (EC 3.5.1.14) $Co(Ac)_2$, 37°C, 24 h; 50% yield; i) $LiAlH_4$, THF, reflux, 2 h, 70% yield.

of compound **13** in NaOH at reflux failed because of the decomposition of the reaction product. Finally the reduction of the acid group rendered the (2*S*, 4*E*)-2-aminocta-4,7-dien-ol (**2**) in 20% overall yield.

The hydrolysis of the (*R*) N-acetyl-aminoacid (**13**) and reduction to alcohol group provided the (2*R*, 4*E*) aminoalcohol **2**.

Our results indicated that *rac*-aminoacid synthesis is more useful than the Schlosser method to construct *E* aminoalcohol **2** because the sequence is shorter and overall yield is higher.

EXPERIMENTAL

General Methods

Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu spectrophotometer. NMR spectra were recorded on Bruker Advance DPX-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz). Chemical shifts are relative to TMS as internal standard. Low-resolution mass spectra (MS) were obtained on a GCMS Shimadzu QP 1100-EX spectrometer. Elemental analyses were obtained from vacuum-dried samples and performed on a Fisons EA 1108 CHNS-O analyzer. Flash column chromatography was carried out with silica gel 60 (J. T. Baker, 40-μm average particle diameter). All reactions and chromatographic separations were monitored by TLC analyses, conducted on 0.25-mm silica-gel plastic sheets (Macherey–Nagel, Polygram^R SIL G/UV 254). Spots were visualised under 254-nm illumination, by iodine vapor, p-hydroxybenzaldehyde spray, or ninhydrine spray. All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) pure compounds. The *Z*/*E* ratio was determined by NMR spectroscopy on the crude reaction mixture.

(4*R*)-4-Hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (4). To a stirred solution of **3** (2.6 g, 9.7 mmol) in MeOH (23 mL) was added in portions $NaBH_4$ (1.2 g, 32 mmol) at rt. After 12 h, the solvent was evaporated. To the residue, 5% HCl was added until pH 7. The aqueous layer was extracted (5 × 30 mL) with AcOEt and the combined organic layer dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (silica gel, AcOEt/*n*-hexane, 1:2) afforded 2.2 g (90%) of **4**.

(4*R*)-4-Methanesulfonyloxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (5c). To a solution of **4** (3.3 g, 14.3 mmol) in pyridine (47 mL) at 0°C was added MsCl (2.24 mL, 14.8 mmol) and the mixture was stirred at 0°C for 1 h and then at 40°C for 4 h. Two percent HCl (100 mL) was added and the mixture extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with 2% HCl

(100 mL), saturated $NaHCO_3$ (2 × 100 mL), and H_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (silica gel, AcOEt/*n*-hexane, 1:2) afforded **5c** (3.9 g, 90%). mp: 75–76°C, Rf = 0.40 (AcOEt/*n*-hexane, 1:2). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (bs, 9H), 1.54 (s, 6H), 1.63 (s, 6H),* 3.03 (s, 3H), 3.99 (d, $J = 3.05$ Hz, 2H), 4.08–4.16 (m, 2H), 4.32–4.34 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 152.6, 151.7,* 94.7,* 94.2, 81.4, 81.1,* 67.6, 65.3,* 65.0, 56.2, 37.9,* 37.6, 28.7, 27.7, 27.1,* 24.6, 23.3.* (* Asterisk denotes minor conformer peaks.) EIMS, 70 eV (%): 294 ([M-15]$^+$, 2.9), 194 (60.8), 138 (14.8), 57 (100). IR (KBr): $\nu = 3380$, 1680, 1520 cm^{-1}. Anal. calc. for $C_{12}H_{23}NO_6S$: C, 46.59; H, 7.49; N, 4.53; S, 10.36. Found: C, 46.13; H, 7.65; N, 4.19; S, 10.77.

(4*R*)-4-Cyanomethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (6). To a solution of **5c** (7 g, 22.7 mmol) in DMF (170 mL) was added KCN (2.07 g, 31.8). The stirred reaction mixture was heated at 90–95°C for 10 h, then washed with water (100 mL), and extracted with AcOEt (9 × 80 mL) and $CHCl_3$ (3 × 70 mL). The combined organic layer was washed with water (80 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (AcOEt/*n*-hexane, 1:2) afforded compound **6** (3.70 g, 70%). Solid, mp 85–87°C, $R_f = 0.60$ (AcOEt/*n*-hexane, 1:2); ^{1}H-NMR ($CDCl_3$) δ: 1.47 (bs, 9H), 1.58 (s, 6H), 1.63 (s, 3H), 2.72 (m, 2H), 3.92 (m, 1H), 4.09 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 152.4, 151.4,* 117.0, 95.2,* 94.7, 81.5, 81.3,* 67.2, 66.8,* 54.5, 54.2,* 28.7, 27.7, 27.1, 24.7, 24.0,* 22.4,* 21.4. (* Asterisk denotes minor conformer peaks.) EIMS (20 eV), *m/z* (%), 225 (M$^+$ -CH_3, 3.1), 125 (21.6), 57 (34.6), 44 (100.0). IR film ν_{max}: 3402, 2254, 1690. Anal. elem. calcd. for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.77; H, 8.63; N, 11.88.

(4*R*)-2,2-Dimethyl-4-(2-oxo-ethyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester (7). To a stirred solution of compound **6** (1.8 g, 7.5 mmol) in CH_2Cl_2 (45 mL) at −40°C was added a solution of 1 M of DIBAL-H in hexane (13 mL, 12.9 mmol) in portions. After 2 h of stirring, MeOH (9 mL) was added carefully and the mixture was allowed to warm up to room temperature. The mixture was then poured into a solution of potassium sodium tartrate (18.2 g) in H_2O (48 mL) and the biphasic mixture stirred vigorously for 2 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on SiO_2 (AcOEt/*n*-hexane, 1:3) to give compound **7** (1.3 g, 70% yield). Oil, $R_f = 0.58$ (AcOEt/*n*-hexane, 1:2). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.57 (s, 6H), 1.62* (s, 6H), 2.59–2.78 (m, 2H), 2.81–3.07* (m, 2H), 3.75 (dd, $J_1 = 1.56$, $J_2 = 9.2$ Hz, 1H), 4.09 (dd, $J_1 = 1.6$, $J_2 = 9.1$ Hz, 1H), 4.06-4.10 (dd $J_1 = 6$, $J_2 = 9.1$ Hz, 1H), 4.30 (bs, 1H), 4.38* (bs, 1H), 9.81 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 200.8, 151.7, 151.7,* 94.4,* 93.8, 81.0, 80.7,* 68.3,* 67.2, 53.1, 52.7,* 48.7,* 47.8, 28.8, 27.9, 27.1,* 24.9, 23.5*. (* Asterisk denotes minor conformer peaks.) EIMS (20 eV), *m/z* (%), 244 ([M + 1]$^+$, 10.5), 243 (M$^+$, 0.2), 228 (9.8), 188 (7.9), 172 (12.8), 144 (33.4), 128

(15.1), 57 (100), 44 (78.5). IR film ν_{max}: 3442.2, 1697.6. Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.99; H, 8.81; N, 5.80.

Triphenylhomoallylphosphine bromide (8). To a solution of 4-bromobutene (5 g, 37 mmol) in toluene (25 mL) was added PPh_3 (9.71 g, 37 mmol). The reaction mixture was stirred at 100°C for 24 h, cooled, filtered, and washed with toluene. The solid was dried for 1 h at 50°C and then overnight in a vacuum dessicator. The resulted salt **13** (10 g, 68%) was used without further purification.

(4*S*, 2*Z*)-4-Hexa-2,5-dienyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (9). Method A (Boden).

To a suspension of salt **8** (983 mg, 2.5 mmol) in CH_2Cl_2 (1.5 mL) was added K_2CO_3 (2.5 mmol, 341 mg) and 18-crown-6 (4.2 mg). The mixture reaction was stirred for 30 min and then a solution of compound **7** (1.65 mmol, 400 mg) in CH_2Cl_2 (1 mL) was added dropwise and refluxed for 4 h. The reaction mixture was cooled, filtered through celite, and washed with Et_2O. The filtrate was concentrated and chromatographed on SiO_2 (AcOEt/*n*-hexane, 1:6) to give alkenyl **9** (632 mg, 90% yield, *Z*/*E*: 90/10). Oil, $R_f = 0.69$ (AcOEt/*n*-hexane, 1:6). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (bs, 9H), 1.60 (bs, 3H), 1.61 (bs, 6H), 1.63* (bs, 3H), 2.20–2.57 (m, 2H), 2.87 (dd, $J_1 = J_2 = 6.6$ Hz, $2H_3$), 3.74–3.93 (m, 3H), 5.00–5.09 (m, 2H), 5.38–5.48 (m, 1H), 5.50–5.57 (m, 1H), 5.76–5.89 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 153.0, 136.9, 130.2, 126.5, 115.3, 94.3, 93.8,* 80.3, 80.2,* 66.9, 66.8,* 57.6, 32.0, 31.5, 30.7,* 28.9, 27.9, 27.1,* 24.9,* 23.7. (* Asterisk denotes minor conformer peaks.) EIMS (20 eV), *m*/*z* (%), 281 (M^+, 0.1), 200 (19.1), 100 (40.7), 83 (4.5), 57 (100). IR ν max = 3410, 1690 cm^{-1}. Anal. calcd. for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 67.99; H, 9.80; N, 5.09.

(4*S*, 2*Z*)-4-Hexa-2,5-dienyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (9). Method B (Hase).

A stirred mixture of salt **8** (0.19 mmol, 74 mg), K_2CO_3 (0.18 mmol, 26 mg), aldhehyde **7** (0.12 mmol, 30 mg), sodium thioglycolate (0.012 mmol, 1.4 mg), dioxane (1 mL), and H_2O (3×10^{-3} mL) were heated to reflux under tungsten daylight lamp irradiation (75 W). After 20 h, the volatiles were removed under reduced pressure and the residue chromatographed on SiO_2 (AcOEt/*n*-hexane, 1:6) to give compound **9** (32 mg, 60% yield, *Z*/*E*: 75/25).

(4*S*, 2*E*)-4-Hexa-2,5-dienyl-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (9). Method C (Schlosser).

To a suspension of salt **8** (0.82 mmol, 326 mg) in THF (2 mL) cooled at −78°C was added PhLi (0.82 mmol, 1.06 M) and the mixture was stirred for 30 min. Then a solution of aldehyde **7** (0.82 mmol, 200 mg) in Et_2O (2 mL) was added dropwise. The mixture turned orange after 45 min, and then more PhLi (0.82 mmol, 1.06 M) was added and the reaction was allowed to warm up to −30°C. At this temperature, *t*BuOK-*t*BuOH (complex 1:1) (229 mg, 1.23 mmol) was added and the mixture was stirred for another 45 min and then filtered through celite, washed with Et_2O, and concentrated in vacuo. Purification by flash comatography on SiO_2 (AcOEt/*n*-hexane,

0.5:5) afforded compound **9** (46 mg, 20% yield, *Z*/*E*:13/87). Oil, $R_f = 0.69$ (AcOEt/*n*-hexane, 1:6).^{1}H-NMR ($CDCl_3$) δ: 1.50 (bs, 9H), 1.60 (bs, 6H), 2.22* (m), 2.47 (m, 2H), 2.77 (m, 2H), 3.78 (dd $J_1 = 8.2$, $J_2 = 17$ Hz, 1H), 3.91 (dd, $J_1 = 8.2$, $J_2 = 5.7$, 1H), 4.99–5.04 (m, 2H), 5.35–5.47 (m, 1H), 5.51–5.62 (m, 1H), 5.79–5.86 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 153.4, 137.3, 131.5, 130.2, 127.6, 126.5, 115.4, 66.9, 57.6, 37.1, 30.1, 28.7. (* asterisk denotes minor conformer peaks.) EIMS (20 eV), *m*/*z* (%), 281 (M^+, 0.3), 200 (22.7), 166 (1.7), 144 (12.3), 100 (42.8), 83 (4.5), 57 (100.0).

(2*R*, 4*Z*)-2-Amino-octa-4,7-dien-1-ol (2). To a solution of (2*R*, 4*Z*) compound **9** (310 mg, 1.1 mmol) in MeOH (30 mL) was added 10% HCl (15 mL). The reaction mixture was stirred at 40°C for 6 h, quenched with saturated solution of $NaHCO_3$, and extracted with AcOEt (6 × 20 mL). The combined organic layer was dried, filtered, concentrated in vacuo, and the residue chromatographed on SiO_2 (AcOEt/*n*-hexane, 1:4) to give (2*R*, 4*Z*) compound **2** (139 mg, 90% yield). Oil, $R_f = 0.43$ ($CHCl_3$/MeOH 2:0.5). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (bs, 1H), 2.09–2.18 (m, 2H), 2.83 (dd, $J_1 = J_2 = 6.1$ Hz, 2H), 2.90 (m, 1H), 3.34 (dd, $J_1 = 7.3$, $J_2 = 10.6$ Hz, 1H), 3.60 (dd, $J_1 = 3.6$, $J_2 = 10.6$ Hz, 1H), 4.98–5.08 (m, 2H), 5.46–5.50 (m, 1H), 5.19–5.50 (m, H), 5.78–5.85 (m, 1H); ^{13}C-NMR ($CDCl_3$,) δ: 137.0, 130.1, 127.2, 115.2, 66.9, 53.1, 32.6, 32.0; EIMS 20 eV, *m*/*z* (%): 141 (M^+, 0.1), 123 (M^+-H_2O, 0.4), 110 (M^+-CH_2OH, 12.5), 74 (8.7), 60 (100.0). IR(film) ν_{max} 3422, 1637 cm^{-1}. $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.45; H, 9.62; N, 11.63.

(2*R*, 4*E*)-2-Amino-octa-4,7-dien-1-ol (2). To a solution of (2*R*, 4*E*) compound **9** (310 mg, 1.1 mmol) in MeOH (30 mL) was added 10% HCl (15 mL). The reaction mixture was stirred at 40°C for 6 h,quenched with saturated solution of $NaHCO_3$, and extracted with AcOEt (6 × 20 mL). The combined organic layer was dried, filtered, concentrated in vacuo, and the residue chromatographed on SiO_2 (AcOEt/*n*-hexane, 1:4) to give (2*R*, 4*E*) compound **2** (137 mg, 89% yield).Oil, Rf = 0.43 ($CHCl_3$/MeOH 2:0.5), ^{1}H-NMR (MeOD) δ: 2.36-2.41 (m, 2H), 2.82 (dd, $J_1 = J_2 = 5.9$ Hz, 2H), 3.22–3.26 (m, 1H), 3.56 (dd, $J_1 = 7.0$, $J_2 = 11.6$ Hz, 1H), 3.77 (dd, $J_1 = 3.7$, $J_2 = 11.6$ Hz, 1H), 5.00–5.04 (m, 1H), 5.48 (m, 1H), 5.82–5.88 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 137.1, 132.1, 127.1, 115.7, 65.7, 53.0, 37.0, 30.1. EIMS (20 eV), *m*/*z* (%), 141 (M^+, 0.1), 123 (M^+-H_2O, 0.42), 110 (M^+-CH_2OH, 12.5), 74 (8.7), 60 (100). IR (film) ν_{max} 3422, 1637 cm^{-1}. Anal. calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.95; H, 9.79; N, 10.29.

(4*E*) 6-Bromo-hexa-1,4-diene (10). To a stirred solution of (4*E*)-6-hydroxy-hexa-1,4-diene (6.3 g, 0.65 mol) in CH_2Cl_2 (80 mL) cooled at −15°C was added CBr_4 (222 g, 0.67 mol) and PPh $_3$ (18 g, 0.67 mmol). After stirring 2 h, the solvent was removed under reduced pressure and the residue chromatographed on SiO_2 (AcOEt/*n*-hexane, 0.25:5) to give alkenyl-bromide **10** (9.3 g, 90%).Oil, $R_f = 0.52$ (AcOEt/*n*-hexane, 0.25:5); ^{1}H-NMR ($CDCl_3$) δ: 2.84 (t, $J = 6.3$ Hz, 2H), 3.98–3.97 (m, 2H), 5.05–5.10 (m, 2H),

5.72–5.85 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ: 137.9, 134.2, 132.2, 116.5, 36.4, 33.4. EIMS (20 eV), m/z (%), 160 (M^+, 0.5), 162 ($M^+ + 2$, 0.4).

(2*E*)-2-Acetylamino-2-hexa-2,5-dienyl-malonic acid diethyl ester (12). To a suspension of Na° (1.3 g, 55.8 mmol) in EtOH (25 mL) a solution of compound **11** (8 g, 36.4 mmol) in EtOH (15 mL) was added. The mixture was stirred at reflux for 45 min and then cooled at room temperature. Bromide **10** (6 g, 37.2 mmol) was added dropwise. The mixture was refluxed for 8 h. H_2O (20 mL) was added and the aqueous layer was extracted with AcOEt (4 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (silica gel, AcOEt/*n*-hexane, 1:2) afforded **12** (8.8 g, 80% yield). Oil, Rf = 0.75 (AcOEt/*n*-hexane, 1:1); ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, J = 7.1 Hz, 6H), 2.03 (s, 3H), 2.73 (t, J = 36.4 Hz, 2H), 3.04 (m, 2H), 4.24 (c, J = 7.1 Hz, 4H), 4.97–5.02 (m, 2H), 5.20–5.24 (m, 1H), 5.49–5.55 (m, 1H), 5.73–5.79 (m, 1H), 6.72 (s, 1HNH); ^{13}C-NMR ($CDCl_3$) δ: 169.2, 168.1, 136.9, 133.8, 124.2, 115.7, 66.8, 62.9, 37.0, 36.2, 23.4, 14.4. EIMS (70 eV), m/z (%), 297 (M^+, 2.5), 252 (M^+ -OEt, 7.7), 224 (13.3), 197 (50.3), 182 (42.5), 174 (48.7), 146 (23.5), 108 (22.5), 43 (100).

(4*E*) *rac*-2-Acetylamino-octa-4,7-dienoic acid (13). A solution of alkenyl ester **12** (1.3 g, 4.4 mmol) in NaOH 2N (25 mL) was stirred overnight at room temperature. The mixture was cooled at 4°C, acidulated with HCl to pH 1, and concentrated in vacuo. The residue was washed with MeOH and filtered. The solution was concentrated in vacuo to 30 mL. H_2O (24 mL) was added and the mixture was refluxed for 6 h. The solvent was removed under reduced pressure. Flash chromatography (silica gel, $CHCl_3$/MeOH/AcOH,3:0.3:0.01) afforded **13** (695 mg, 80% yield). Oil, Rf = 0.58 ($CHCl_3$/MeOH/AcOH, 3:0.3:0.01). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (s, 3H), 2.52–2.76 (m, 3H), 4.62–4.71 (m, 1H), 4.98–5.03 (m, 2H), 5.35–5.39 (m, 1H), 5.56–5.59 (m, 1H), 5.76–5.82 (m, 1H), 6.10–6.42 (m, 1HNH). ^{13}C-NMR ($CDCl_3$) δ: 175.1, 171.7, 136.9, 133.4, 124.9, 116.3, 52.6, 36.9, 35.3, 23.3. EIMS (70 eV), m/z (%), 197 (M^+, 0.8), 182 (5.5), 120 (22.7), 117 (19.1), 110 (16.8), 99 (29.1), 97 (39.7), 74 (100.0). Anal. elem. calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.21; H, 7.15; N, 6.95.

(2*S*, 4*E*) 2-Amino-octa-4,7-dienoic acid (14). To a solution of compound **13** (200 mg, 1.1 mmol) in H_2O (10 mL) was added NH_4OH (conc.) to pH 7.5, acylasa I (EC 3.5.1.14) (1 mg), and cobalt acetate (2 mg). After 20 h at 37°C more acylasa (0.1 mg) was added and the hydrolysis continued for 4 h. The mixture was concentrated in vacuo. Flash chromatography (silica gel, $CHCl_3$/MeOH/NH_3, 1.5:1.5:0.1) afforded **14** (85 mg, 50% yield). Solid, mp 52–53°C. ^{1}H-NMR (MeOD) δ: 2.53–2.63 (m, 2H), 2.67–2.75 (m, 2H), 3.74–3.76 (m, 1H), 5.02–5.09 (m, 2H), 5.39–5.43 (m, 1H), 5.72–5.76 (m, 1H), 5.87–5.91 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 174.1, 137.7, 123.9, 115.7, 54.8, 36.4, 34.1.

(2*S*, 4*E*)-2-Amino-octa-4,7-octadien-1-ol (2). To a suspension of **14** (80 mg, 0.5 mmol) in THF (15 mL) cooled at 4°C was added $LiAlH_4$ (100 mg,

2.6 mmol) in portions. The mixture was heated to reflux for 3 h and the excess of $LiAlH_4$ was destroyed with cooled AcOEt. The mixture was filtered through celite and washed with MeOH. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 3:0.5) to afford (2*S*, 4*E*) **2** (49 mg, 70% yield). The spectroscopic data were in agreement with those of aminoalcohol **2** synthesised previously by Schlosser's methodology.

CONCLUSIONS

In conclusion, we have developed two methodologies to obtain aminoalcohols **2**, intermediates of mycothiazole, and their reduced analogs with different stereochemistry.

The method that involves the homologated Garner's aldehyde gave (2*R*, 4*Z)*-**2**-aminocta-4,7-dien-ol (**2**) in high yield. In contrast, the (2*R*, 4*E)* compound **2** was obtained in a moderate yield.

The aminoacid strategy provides the (2*S*, 4*E*) aminoalcohol **2** in good yield.

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