Triazole Antifungals. V.[1] Synthesis and Antifungal Activities of Some Amides Related to 3-Acylamino-2-aryl-1-triazolyl-2-butanol

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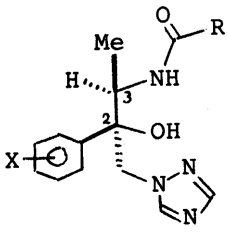
Amides, 2 and 3, related to the potent antifungal triazole-amide 3-acylamino-2-aryl-1-triazolyl-2-butanol (1) were synthesized starting from the triazole-alcohol 6. The antifungal activity of 2 and 3 against a mouse systemic *Candida albicans* infection was found to be less potent than that of 1.

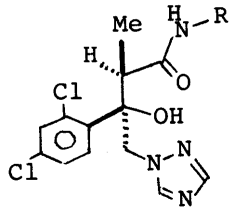
Keywords antifungal activity; 1,2,4-triazole; 3-carbamoyl-2-aryl-1-(triazol-1-yl)-2-butanol; 4-acylamino-2-aryl-3-methyl-1-(triazol-1-yl)-2-butanol; structure–activity relationship; β-lactone; stereochemistry assignment

In a preceding paper,[1] we reported the synthesis and antifungal activities of a series of 3-acylamino-2-aryl-1-triazolyl-2-butanols (**1**). Remarkably potent *in vivo* activity was observed in **1**, in which R is a substituted-phenyl or -styryl group, against a mouse systemic *Candida albicans* infection. The 2*R*,3*R* absolute configuration, as well as the location of the methyl group at the C(3) position of **1**, was demonstrated to be a key structural element of antifungal potency. A structural similarity between **1** and lanosterol, a natural substrate of the cytochrome P-450 14α-demethylase, and the potential ability of **1** to inhibit this enzyme in the fungal biosynthesis of ergosterol were hypothesized as accounting for the potent activities of **1**.

In connection with structure–activity relationship studies in this series of compounds, we were interested in new types of triazoles, *i.e.* the amides **2**, in which the arrangement of the carbon–nitrogen linkage of the amide group is reversed as compared with that in **1** (hereinafter referred to as "reversed amides"), and the homolog amides **3**, in which a methylene group was added by insertion between the C(3) carbon and the nitrogen atom in **1**. Triazoles **2** and **3** with *threo* stereochemistry were of interest, because they have the same stereochemical relationship as the original amides **1**. In this paper we report the synthesis of **2** and **3** and their antifungal activities.



1 : X=halogen (s)



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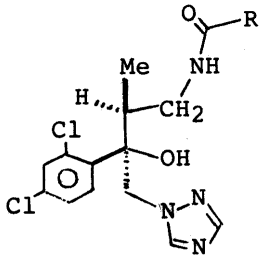

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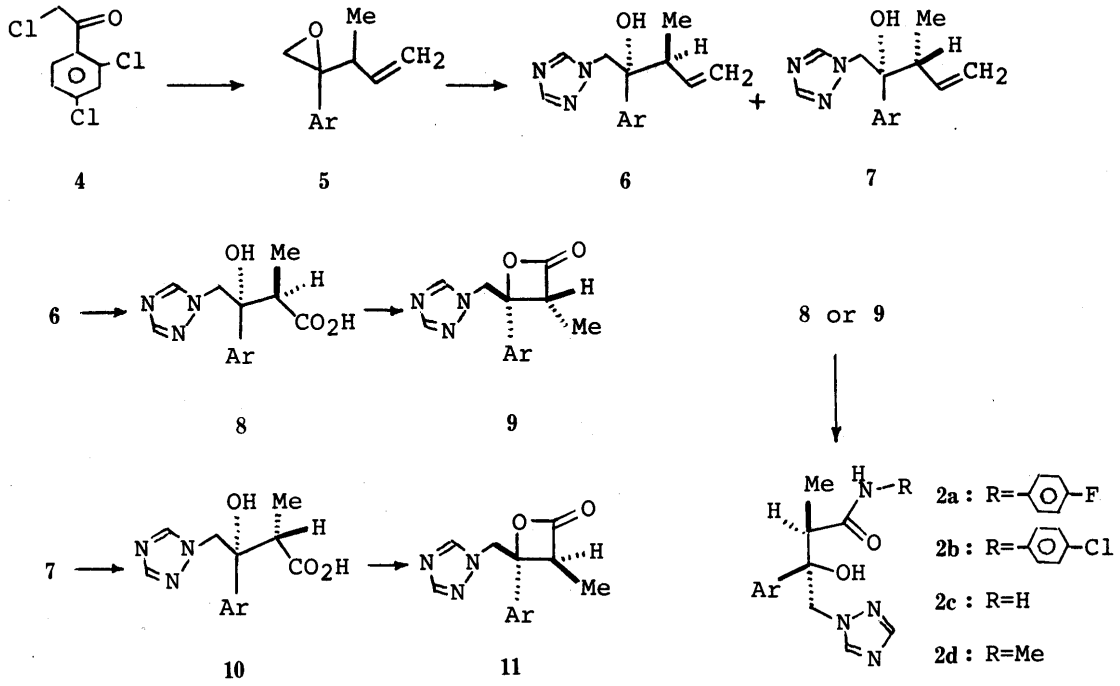
Chart 1

Triazole-alcohol **6** was chosen as a starting material for the synthesis of **2** and **3**, since it has the required stereochemistry to lead to such *threo* stereoisomers. The preparation of **6** and its diastereomer **7** has been described in a patent,[2] although the stereochemistry of these alcohols has not been determined. According to the patent procedure with slight modification, the triazoles, **6** and **7**, were provided. Thus, 2,2',4'-trichloroacetophenone (**4**) was treated with the Grignard reagent prepared from 1-chloro-2-butene and magnesium, and then the resulting epoxide **5** was ring-opened by reaction with sodium triazolide to afford **6** and **7** in approximately a 3 : 2 ratio, which were separated by column chromatography. To determine the stereochemistry of these azoles, **6** and **7** were transformed into the β-lactones **9** and **11**, respectively, as follows. Oxidation of **6** with $KMnO_4$ in H_2SO_4–aqueous acetone afforded the carboxylic acid **8** in 75% yield. Diastereomer **7** was also oxidized to acid **10** in 88% yield in an alternative manner by treatment with a catalytic amount of $KMnO_4$ in the presence of $NaIO_4$ in aqueous acetone. Carboxylic acids, **8** and **10**, were treated with *N*-hydroxysuccinimide and *N*,*N*'-dicyclohexylcarbodiimide (DCC),[3] and then with triethylamine to afford respectively the β-lactones **9** (72%) and **11** (90%). The stereochemistry of **9** and **11** was assigned based on proton nuclear magnetic resonance (^{1}H-NMR) spectral analysis. The ^{1}H-NMR signal of the methyl group of **11** was observed at δ 1.70, whereas that of **9** appeared at δ 1.22, significantly shifted upfield. This suggests proximity (*cis* orientation) of the methyl group and the aryl group in **9**. This assignment of stereochemistry was supported by differential nuclear Overhauser enhancement (NOE) experiments of **9** and **11** (Fig. 1), which indicated a *cis* arrangement of 3-H and the methylene group of the 4-(triazolylmethyl) group in **9**, and proximity of the 3-methyl group and one of the 4-methylene protons in **11**.

It is noteworthy that marked differences in chemical shifts of the methyl groups, as was observed between the β-lactones **9** and **11**, were also observed between noncyclic series of the *threo* and *erythro* olefin-alcohols, **6** and **7**, and their derivatives described above, and also between the amides **1** and their corresponding diastereomers. The results are summarized in Table I. The *threo* olefin **6**, its derivatives (**8**, **12**, and **13**) and the *threo* amide **1a** (**1**: X=Cl_2, R=4-



Ar = 2, 4-dichlorophenyl

Chart 2

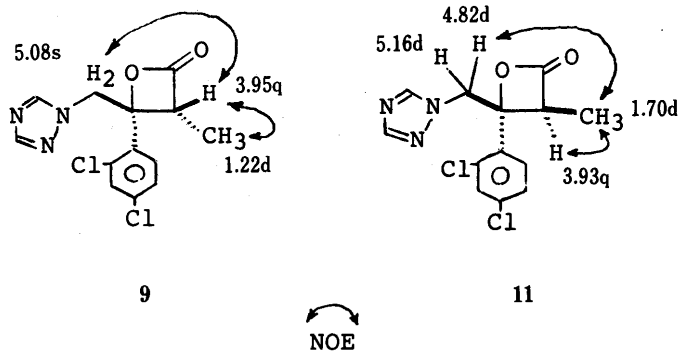
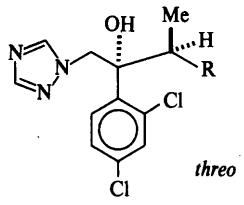
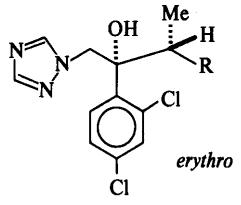


Fig. 1. NOEs Observed in NOE Difference Spectra of **9** and **11**

TABLE I. Comparison of Chemical Shifts of the Methyl Signals between *threo* and *erythro* Derivatives (in $CDCl_3$)



Compd.	R	δ (Me)
6	$CH=CH_2$	0.78
8	COOH	0.77[a]
12	CHO	0.96
13	CH_2OH	0.77[b]
1a	NHCO-(4-Cl-C$_6$H$_4$)	0.95



Compd.	R	δ (Me)
7	$CH=CH_2$	1.29
10	COOH	1.33[a]
14	CHO	1.40
15	CH_2OH	1.39
1a'	NHCO-(4-Cl-C$_6$H$_4$)	1.45

a) In DMSO-d_6. *b*) In a 1 : 1 mixture of $CDCl_3$ and CD_3OD.

ClC_6H_4) showed their methyl signals at a higher field than the corresponding *erythro* isomer **7**, its derivatives (**10**, **14**, and **15**) and the *erythro* amide **1a'**. This provides useful criteria to infer the *threo* and *erythro* configuration of 3-substituted 2-aryl-1-triazolyl-2-butanols.

Acid **8** was treated with 4-fluoroaniline in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline[4] in *N*,*N*-dimethylformamide (DMF) to afford anilide **2a** in 47% yield. The 4-chloroanilide **2b** was similarly obtained by reaction of **8** and 4-chloroaniline. The simple amide **2c** was prepared in 49% yield by treatment of **8** with *N*-hydroxysuccinimide and DCC in tetrahydrofuran (THF) followed by reaction with NH_3. The *N*-methylamide **2d** was obtained from the lactone **9** by treatment with methylamine in MeOH–chloroform at 60 °C in 63% yield.

Amides **3**, which correspond to homologs of **1**, were synthesized in the following manner (Chart 3). Olefin-alcohol **6** was oxidized with a catalytic amount of OsO_4 and excess $NaIO_4$ to afford aldehyde **12**, which was reduced to diol **13** by $NaBH_4$ treatment. In a similar manner, diastereomer **7** was converted to aldehyde **14**, and then to diol **15**. Diol **13** was transformed into aminoalcohol **18** *via* **16** and **17** in a usual manner. Acylation of **18** with 4-(trifluoromethyl)benzoyl chloride and 4-chlorocinnamoyl chloride gave amides **3a** and **3b**, respectively.

The antifungal activity of **2** and **3** was evaluated in a mouse model of a systemic *Candida albicans* infection. The results are summarized in Table II. In the experiment, the compounds were administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, and 24 h post-infection. All control mice (no drug) died within 2 d after infection. The antifungal efficacy of the compounds was compared with that of ketoconazole and also with that of typical samples of 3-acylamino-2-aryl-1-triazolyl-2-butanols, **1a** and **1b** [**1**: X = 2,4-Cl_2, R = 4-$(CF_3)C_6H_4$].

When the antifungal activity of reversed amides **2** was compared to that of amides **1**, the former compounds were found to be considerably less active. The anilide derivatives

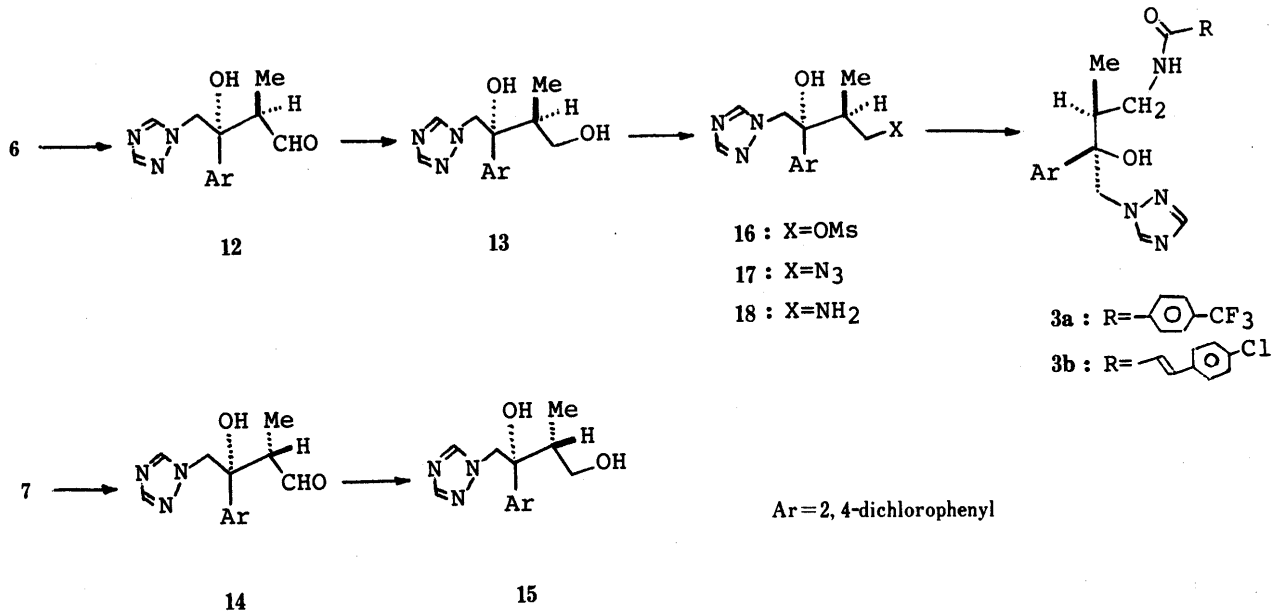
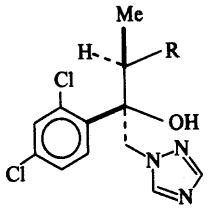


Chart 3

TABLE II. Comparison of the Antifungal Efficacy of "Reversed Amides" (**2a—d**) and Homolog Amides (**3a, b**) with Parent Amides (**1a, b**) against Systemic Infection of *Candida albicans*[a]



Compd.[b]	R	Dose (mg/kg)	Route	% survival rate on day 3	9	14	21
2a	CONH-(C6H4)-F	20	*p.o.*	20	20	0	
			i.p.	30	20	10	10
2b	CONH-(C6H4)-Cl	20	*p.o.*	0			
			i.p.	0			
2c	$CONH_2$	20	*p.o.*	80	80	80	40
			i.p.	40	40	30	10
2d	CONHMe	18	*p.o.*	90	90	50	20
			i.p.	50	40	30	10
3a	CH_2NHCO-(C6H4)-CF_3	20	*p.o.*	100	80	70	60
			i.p.	100	40	40	30
3b	CH_2NHCO-(Cl)-CH=CH-	17	*p.o.*	100	60	40	40
			i.p.	80	30	20	20
1a	NHCO-(C6H4)-Cl	20	*p.o.*	100	100	70	30
			i.p.	100	100	100	80
1b	NHCO-(C6H4)-CF_3	20	*p.o.*	100	100	100	100
			i.p.	100	100	100	100
Ketoconazole		20	*p.o.*	100	60	30	20
			i.p.	90	40	30	10
Control (no drug)				0			

a) *In vivo* activity was determined in mice (each group consisted of ten male mice, 5 weeks old, of the ddY strain) that were infected systemically using an intravenous challenge of 6 to 9×10^6 cells of *Candida albicans* 427. The triazole was administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, and 24 h post-infection. *b*) All compounds are racemic. The amides **3a** and **3b** are oxalic acid salts and other triazoles are free bases.

with either a 4-fluoro (**2a**) or 4-chloro (**2b**) substituent exhibited no significant activity, which contrasts with the potent activity of 4-chlorobenzamide **1a**. Simple amide **2c** and its *N*-methyl analog **2d** were somewhat active, comparable to ketoconazole, although they were less potent than **1a** and **1b**.

Homolog amides **3a** and **3b** showed more potent oral activity than ketoconazole. However, their potency was inferior to that of parent amides **1a** and **1b**.

In conclusion, the antifungal activity of reversed amides **2** and homolog amides **3** related to 3-acylamino-2-aryl-1-triazolyl-2-butanol **1** was found to be less potent than that of **1**. This result is presumed to be mainly due to a less favorable conformation of **2** and **3** to align to fit to the lanosterol skeleton than does the conformation of **1**.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-2 spectrometer and ^{1}H-NMR spectra on a Varian EM-360L spectrometer (60 MHz), or a JEOL GX-270 spectrometer (270 MHz) using Me_4Si as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS D300 spectrometer. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel 60 F_{254} precoated, layer thickness 0.25 mm (E. Merck), and spots were made visible by ultraviolet (UV) irradiation, by spraying with vanadic acid–sulfuric acid followed by heating, or by iodine treatment. Column chromatography was performed on silica gel (60—110 mesh, Kanto Chemical Co., Inc.), and flash column chromatography was performed on silica gel (Kieselgel 60 Art. 9385, 230—400 mesh, E. Merck). The amount of silica gel used and the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; dq, doublet of quartets; t, triplet; q, quartet; qd, quartet of doublets; m, multiplet; br, broad.

(2*R,3*S**)-2-(2,4-Dichlorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-4-penten-2-ol (6) and the (2*R**,3*R**) Diastereomer (7)** A mixture of magnesium (250 mg, 10.3 mmol), 1-chloro-2-butene (100 mg, 1.10 mmol), 1,2-dibromoethane (trace amount) and THF (1 ml) was stirred at room temperature under an N_2 atmosphere. After the reaction started, the mixture was cooled to 0 °C and a solution of 1-chloro-2-butene (805 mg, 9.0 mmol) in THF (7 ml) was added to this mixture over a period of 20 min. Stirring was continued for an additional 30 min at the same temperature, and then a solution of 2,2',4'-trichloroacetophenone (**4**, 1.66 g, 7.43 mmol) in THF (2 ml) was added over a period of 10 min. After 30 min, a saturated aqueous solution of NH_4Cl was added at 0 °C, and the mixture was extracted with hexane. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product **5** (1.83 g, *ca.* 100%) as an oil, which was used without further purification for the next reaction. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.03,

1.05 (3H each, d, J=6.5 Hz), 2.68, 2.72 (1H each, d, J=5 Hz), 3.12, 3.14 (1H each, d, J=5 Hz), 2.6—3.2 (2H, m), 4.5—5.2 (6H, m), 7.0—7.5 (6H, m).

1,2,4-Triazole (1.00 g, 15.0 mmol) was slowly added to a suspension of sodium hydride (55% mineral oil dispersion, 570 mg, 13.1 mmol, washed with hexane) in DMF (15 ml), with stirring at 0 °C. When the hydrogen gas ceased to evolve, a solution of the crude epoxide **5** (1.83 g, 7.40 mmol) in DMF (3 ml) was added. The mixture was then stirred at 120 °C for 2 h, after which the mixture was partitioned between benzene and brine. The organic layer was collected, dried and concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (30 g, AcOEt–hexane, 1 : 4, v/v) to afford the less polar isomer **6** (928 mg, 40%) as colorless crystals (recrystallized from benzene–hexane), mp 135—137 °C, and the more polar isomer **7** (643 mg, 28%) as colorless crystals (recrystallized from benzene–hexane), mp 103—105 °C. *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3O$: C, 53.86; H, 4.84; N, 13.46. Found for **6**: C, 53.85; H, 4.76; N, 13.57. Found for **7**: C, 53.96; H, 4.83; N, 13.54. ^{1}H-NMR (60 MHz, $CDCl_3$) δ for **6**: 0.78 (3H, d, J=6.5 Hz), 3.28 (1H, dq, J=9, 6.5 Hz), 4.40 (1H, d, J=14 Hz), 4.5 (1H, br), 5.08 (1H, t, J=2 Hz), 5.16 (1H, dd, J=9, 2 Hz), 5.24 (1H, dd, J=18, 2 Hz), 5.40 (1H, d, J=14 Hz), 6.12 (1H, dt, J=18, 9 Hz), 7.08 (1H, dd, J=8, 2 Hz), 7.29 (1H, d, J=2 Hz), 7.56 (1H, d, J=8 Hz), 7.76 (1H, s), 7.85 (1H, s); for **7**: 1.29 (3H, d, J=6.5 Hz), 3.38 (1H, m), 4.2 (1H, br), 4.49 (1H, d, J=14 Hz), 4.76 (1H, dd, J=10, 2.5 Hz), 4.78 (1H, dd, J=18, 2.5 Hz), 5.43 (1H, d, J=14 Hz), 5.60 (1H, ddd, J=18, 10, 8 Hz), 7.02 (1H, dd, J=8, 2 Hz), 7.26 (1H, d, J=2 Hz), 7.44 (1H, d, J=8 Hz), 7.74 (1H, s), 7.90 (1H, s).

(2*R,3*R**)-3-(2,4-Dichlorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butyric Acid (8)** A solution of $KMnO_4$ (1.01 g, 6.4 mmol) in H_2O (5 ml) was added to a mixture of **6** (500 mg, 1.60 mmol), 1 M H_2SO_4 (6.4 ml) and acetone (2.5 ml). The whole was stirred at room temperature for 40 h. The precipitates that emerged were filtered off and the filtrate was concentrated under reduced pressure to half the initial volume, which was extracted twice with AcOEt. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give a solid, which was triturated and washed with hexane to afford **8** (395 mg, 75%) as a pale yellow powder. Recrystallization from ether–hexane gave a pure specimen as colorless crystals, mp 195—200 °C. MS *m/z*: 332, 330 (M^++1), 247, 229, 216, 214, 175, 173, 159, 145, 83 (100%). *Anal.* Calcd for $C_{13}H_{13}Cl_2N_3O_3$: C, 47.29; H, 3.97; Cl, 21.48; N, 12.73. Found: C, 47.32; H, 4.02; Cl, 21.33; N, 12.70. IR ν_{max}^{KBr} cm^{-1}: 3395, 1682, 1589. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 0.77 (3H, d, J=7 Hz), 3.68 (1H, q, J=7 Hz), 4.76 (1H, d, J=14.5 Hz), 5.23 (1H, d, J=14.5 Hz), 5.95 (1H, br), 7.22 (1H, dd, J=8, 2 Hz), 7.35 (1H, d, J=8 Hz), 7.51 (1H, d, J=2 Hz), 7.62 (1H, s), 8.36 (1H, s), 12.7 (1H, br).

(3*R,4*R**)-4-(2,4-Dichlorophenyl)-3-methyl-4-(1*H*-1,2,4-triazol-1-yl)-2-oxetanone (9)** DCC (122 mg, 0.59 mmol) was added to a stirred solution of **8** (177 mg, 0.54 mmol) and *N*-hydroxysuccinimide (68 mg, 0.59 mmol) in dioxane (6 ml) and the mixture was stirred at room temperature for 30 min, after which triethylamine (119 mg, 1.18 mmol) was added. After 1 h, the mixture was partitioned between AcOEt and brine. The organic layer was collected and dried. Evaporation of the solvent *in vacuo* gave a solid, which was dissolved in AcOEt–benzene. An insoluble material (*N*,*N*'-dicyclohexylurea) was filtered off. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (9 g, AcOEt) to give **9** (120 mg, 72%) as colorless crystals, mp 131—133 °C. MS *m/z*: 312 (M^++1), 276, 232, 214, 175, 173 (100%), 163, 145, 128, 109, 83. IR ν_{max}^{KBr}: 1835 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.22 (3H, d, J=6.9 Hz), 3.95 (1H, q, J=6.9 Hz), 5.08 (2H, s), 7.34 (1H, dd, J=8.6, 2.0 Hz), 7.43 (1H, d, J=8.6 Hz), 7.53 (1H, d, J=2.0 Hz), 7.90 (1H, s), 8.17 (1H, s).

(2S*,3*R)-3-(2,4-Dichlorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butyric Acid (10)** A solution of **7** (100 mg, 0.32 mmol) in acetone (4 ml) was added to a solution of $NaIO_4$ (342 mg, 1.60 mmol), $KMnO_4$ (5 mg, 0.032 mmol) and K_2CO_3 (70 mg, 0.51 mmol) in water (6 ml). The whole was stirred at room temperature overnight and then concentrated under reduced pressure to half the initial volume. The mixture was neutralized to pH 7 by the addition of 2 N HCl and then acidified to pH 4 by the addition of AcOH. After being saturated with NaCl, this mixture was extracted twice with AcOEt. The combined extracts were washed with brine and dried. Evaporation of the solvent *in vacuo* gave a crystalline residue (105 mg), which was recrystallized from AcOEt–benzene to afford **10** (93 mg, 88%) as colorless crystals, mp 181—182 °C. *Anal.* Calcd for $C_{13}H_{13}Cl_2N_3O_3$: C, 47.29; H, 3.97; N, 12.73. Found: C, 47.54; H, 4.10; N, 12.52. IR ν_{max}^{KBr} cm^{-1}: 3395 (br), 3117, 2490 (br), 1691. ^{1}H-NMR (60 MHz, DMSO-d_6) δ: 1.33 (3H, d, J=6.5 Hz), 3.3—4.0 (1H, br), 3.74 (1H, q, J=6.5 Hz), 4.55 (1H, d, J=14 Hz), 5.12 (1H, d, J=14 Hz), 7.14 (1H, dd, J=8, 2 Hz), 7.42 (1H, d, J=8 Hz), 7.44 (1H, d, J=2 Hz), 7.60 (1H, s), 8.21 (1H, s).

(3*S,4*R**)-4-(2,4-Dichlorophenyl)-3-methyl-4-(1*H*-1,2,4-triazol-1-yl)-2-oxetanone (11)** DCC (43 mg, 0.21 mmol) was added to a stirred solution of **10** (62 mg, 0.19 mmol) and *N*-hydroxysuccinimide (24 mg, 0.21 mmol) in THF (0.6 ml) and the mixture was stirred at room temperature for 30 min, after which triethylamine (42 mg, 0.42 mmol) was added. After 1 h, the mixture was partitioned between AcOEt and brine. The organic layer was collected and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a solid, which was dissolved in AcOEt–benzene. An insoluble material (*N*,*N*'-dicyclohexylurea) was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (5 g, AcOEt–hexane, 2 : 1, v/v) to give **11** (53 mg, 90%), as a crystalline mass, which was recrystallized from AcOEt–benzene to provide an analytical sample as prisms, mp 167—168 °C. *Anal.* Calcd for $C_{13}H_{11}Cl_2N_3O_2$: C, 50.02; H, 3.55; N, 13.46. Found: C, 50.20; H, 3.57; N, 13.49. MS *m/z*: 314, 312 (M^++1), 276, 232, 216, 214, 175, 173 (100%), 145, 98, 83. IR $\nu_{max}^{CHCl_3}$: 1837 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.70 (3H, d, J=7.9 Hz), 3.93 (1H, q, J=7.9 Hz), 4.82 (1H, d, J=14.7 Hz), 5.16 (1H, d, J=14.7 Hz), 6.99 (1H, d, J=8.4 Hz), 7.12 (1H, dd, J=8.4, 2.0 Hz), 7.45 (1H, d, J=2.0 Hz), 7.75 (1H, s), 8.17 (1H, s).

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-(4-fluorophenyl)carbamoyl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (2a)** 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (374 mg, 1.50 mmol) was added to a stirred solution of **8** (500 mg, 1.50 mmol) and 4-fluoroaniline (167 mg, 1.50 mmol) in DMF (8 ml). The mixture was allowed to stand at room temperature for 24 h, after which the mixture was partitioned between AcOEt and water. The organic layer was washed successively with a diluted aqueous solution of $NaHCO_3$, 10% (w/v) citric acid–water and brine. The solvent was evaporated *in vacuo* to give the crude product which was purified by flash column chromatography (12 g, AcOEt–hexane, 1 : 1, v/v) to give **2a** (300 mg, 47%) as a crystalline mass. An analytical sample was obtained as colorless crystals, mp 253—254 °C, by recrystallization from MeOH–AcOEt–hexane. *Anal.* Calcd for $C_{19}H_{17}Cl_2FN_4O_2$: C, 53.92; H, 4.05; Cl, 16.75; F, 4.49; N, 13.24. Found: C, 54.14; H, 4.18; Cl, 16.48; F, 4.29; N, 13.26. MS *m/z*: 424, 422 (M^+), 342, 340, 312, 294, 256, 214, 175, 173 (100%), 159, 145, 138, 111, 95, 83. IR ν_{max}^{KBr} cm^{-1}: 3384, 3256, 1660. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 0.90 (3H, d, J=7.3 Hz), 3.88 (1H, q, J=7.3 Hz), 4.52 (1H, d, J=14.4 Hz), 5.23 (1H, d, J=14.4 Hz), 6.53 (1H, s), 7.17—7.24 (2H, m), 7.27 (1H, dd, J=8.8, 2.0 Hz), 7.48 (1H, d, J=8.8 Hz), 7.56 (1H, d, J=2.0 Hz), 7.57 (1H, s), 7.64—7.69 (2H, m), 8.34 (1H, s), 10.60 (1H, s).

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-(4-chlorophenyl)carbamoyl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (2b)** Following a procedure similar to that described for **2a**, **3a** was obtained as colorless crystals, mp 268—269 °C (recrystallized from AcOEt–hexane), in 20% yield by reaction of **8** and 4-chloroaniline. *Anal.* Calcd for $C_{19}H_{17}Cl_3N_4O_2$: C, 51.90; H, 3.90; N, 12.74. Found: C, 51.87; H, 3.98; N, 12.62. IR ν_{max}^{KBr} cm^{-1}: 3430, 1660. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 0.90 (3H, d, J=6.8 Hz), 3.88 (1H, q, J=6.8 Hz), 4.53 (1H, d, J=14.2 Hz), 5.20 (1H, d, J=14.2 Hz), 6.46 (1H, s), 7.27 (1H, dd, J=8.8, 2.0 Hz), 7.43 (2H, J=8.8 Hz), 7.48 (1H, d, J=8.8 Hz), 7.56 (1H, d, J=2.0 Hz), 7.57 (1H, s), 7.68 (2H, d, J=8.8 Hz), 8.34 (1H, s), 10.65 (1H, s).

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-carbamoyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (2c)** DCC (127 mg, 0.62 mmol) was added to a solution of **8** (185 mg, 0.56 mmol) and *N*-hydroxysuccinimide (71 mg, 0.62 mmol) in dioxane (6 ml), and the mixture was stirred at room temperature for 3 h. NH_3 (gas) was slowly introduced into this mixture (over a period of 3 h). Then the mixture was allowed to stand at room temperature overnight. After the solvent was evaporated under reduced pressure, the residue was dissolved in $CHCl_3$. Insoluble materials were filtered off and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (15 g, $CHCl_3$–MeOH, 20 : 1, v/v) to afford **2c** (90 mg, 49%) as a solid. Recrystallization from AcOEt–hexane gave colorless prisms, mp 206—207 °C (dec.), which were found to contain 1/2 AcOEt by elementary analysis and ^{1}H-NMR. *Anal.* Calcd for $C_{13}H_{14}Cl_2N_4O_2 \cdot$ 1/2AcOEt: C, 48.27; H, 4.86; N, 15.10. Found: C, 48.02; H, 4.76; N, 15.22. MS *m/z*: 331, 329 (M^++1), 248, 246, 231, 229, 216, 214, 175, 173 (100%), 159, 145, 115, 102, 83. IR ν_{max}^{KBr} cm^{-1}: 3436, 3285, 1730, 1667. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 0.80 (3H, d, J=6.8 Hz), 3.67 (1H, q, J=6.8 Hz), 4.39 (1H, d, J=14.2 Hz), 5.17 (1H, d, J=14.2 Hz), 7.04 (1H, s), 7.23 (1H, dd, J=8.5, 2.0 Hz), 7.42 (1H, d, J=8.5 Hz), 7.52 (1H, d, J=2.0 Hz), 7.57 (1H, s), 7.62 (1H, br s), 8.22 (1H, br s), 8.29 (1H, s).

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-(*N*-methylcarbamoyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (2d)** A 40% methylamine solution in MeOH (1 ml) was added to a solution of **9** (110 mg, 0.35 mmol) in $CHCl_3$ (2 ml), and

the whole was heated at 60 °C for 1 h. The mixture was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried and concentrated *in vacuo* to afford a crystalline residue, which was recrystallized from benzene–$CHCl_3$–hexane to give **2d** (76 mg, 63%) as fine prisms, mp 192—195 °C. MS *m/z*: 345, 343 ($M^+ + 1$), 307, 289, 262, 260 (100%), 214, 203, 185, 175, 173, 159, 145, 129, 114, 83. IR ν_{max}^{KBr} cm^{-1}: 3270, 1642. ^{1}H-NMR (60 MHz, DMF-d_7) δ: 0.88 (3H, d, J=7 Hz), 2.80 (3H, d, J=4.5 Hz), 3.78 (1H, q, J=7 Hz), 4.41 (1H, J=14 Hz), 5.20 (1H, d, J=14 Hz), 7.12 (1H, s), 7.2—7.65 (3H, m), 7.51 (1H, s), 8.26 (1H, s), 8.72 (1H, d, J=4.5 Hz).

(2*R,3*R**)-3-(2,4-Dichlorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butanol (12) and the (2*S**,3*R**) Diastereomer (14)** A mixture of **6** (139 mg, 0.45 mmol), $NaIO_4$ (275 mg, 1.30 mmol), OsO_4 (1 mg), H_2O (0.8 ml) and THF (2 ml) was stirred at room temperature overnight. The mixture was diluted with AcOEt, washed with brine and dried. Evaporation of the solvent under reduced pressure gave an oily residue, which was purified by column chromatography (4 g, AcOEt–hexane, 1 : 1, v/v) to give **12** (83 mg, 63%) as a solid. Recrystallization from benzene afforded an analytical sample as colorless crystals, mp 150—151 °C. *Anal.* Calcd for $C_{13}H_{13}Cl_2N_3O_2$: C, 49.70; H, 4.17; N, 13.38. Found: C, 49.83; H, 4.15; N, 13.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1715. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.96 (3H, d, J=7 Hz), 3.47 (1H, qd, J=7, 3 Hz), 4.64 (1H, d, J=14 Hz), 5.42 (1H, d, J=14 Hz), 5.3 (1H, br), 7.11 (1H, dd, J=8, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.52 (1H, d, J=8 Hz), 7.77 (1H, s), 7.85 (1H, s), 9.88 (1H, d, J=3 Hz).

In a similar way, oxidation of **7** gave **14** as a solid in 58% yield. Recrystallization from AcOEt–benzene afforded an analytical sample of **14** as colorless crystals, mp 155—157 °C. *Anal.* Calcd for $C_{13}H_{13}Cl_2N_3O_2$: C, 49.70; H, 4.17; N, 13.38. Found: C, 49.55; H, 4.08; N, 13.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1715. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.40 (3H, d, J=7 Hz), 3.52 (1H, br q, J=7 Hz), 4.50 (1H, d, J=14 Hz), 5.42 (1H, d, J=14 Hz), 7.11 (1H, dd, J=8, 2 Hz), 7.35 (1H, d, J=2 Hz), 7.54 (1H, d, J=8 Hz), 7.75 (1H, s), 7.87 (1H, s), 9.39 (1H, d, J=1.5 Hz).

(2*S,3*R**)-3-(2,4-Dichlorophenyl)-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)-1,3-butanediol (13) and the (2*R**,3*R**) Diastereomer (15)** Sodium borohydride (30 mg, 0.79 mmol) was added to a solution of **12** (160 mg, 0.50 mmol) in methanol (3 ml), with stirring at 0 °C. After 10 min, the mixture was partitioned between AcOEt and brine. The organic layer was collected, dried and concentrated *in vacuo*. The residue was chromatographed (5 g, MeOH–AcOEt, 1 : 20, v/v) to give **13** (145 mg, 88%) as colorless crystals (recrystallized from benzene–hexane), mp 176—177 °C. *Anal.* Calcd for $C_{13}H_{15}Cl_2N_3O_2$: C, 49.38; H, 4.78; N, 13.29. Found: C, 49.25; H, 4.78; N, 13.20. ^{1}H-NMR (60 MHz, $CDCl_3$ + CD_3OD, 1 : 1) δ: 0.77 (3H, d, J=7 Hz), 2.6—3.1 (1H, m), 3.6—4.2 (2H, m), 4.74 (1H, d, J=14.5 Hz), 5.44 (1H, d, J=14.5 Hz), 7.04 (1H, dd, J=8, 2 Hz), 7.30 (1H, d, J=2 Hz), 7.48 (1H, d, J=8 Hz), 7.67 (1H, s), 8.07 (1H, s).

In a similar way, reduction of **14** gave **15**, mp 120—122 °C (recrystallized from benzene–hexane), in 91% yield. *Anal.* Calcd for $C_{13}H_{15}Cl_2N_3O_2$: C, 49.38; H, 4.78; N, 13.29. Found: C, 49.32; H, 4.85; N, 13.23. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.39 (3H, d, J=7 Hz), 2.6—3.0 (1H, m), 3.40 (1H, s), 3.45 (1H, s), 3.7—4.3 (2H, m), 4.50 (1H, d, J=14 Hz), 5.31 (1H, d, J=14 Hz), 7.05 (1H, dd, J=8, 2 Hz), 7.25 (1H, d, J=2 Hz), 7.52 (1H, d, J=8 Hz), 7.66 (1H, s), 7.91 (1H, s).

(2*R,3*S**)-2-(2,4-Dichlorophenyl)-4-methanesulfonyloxy-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16)** Methanesulfonyl chloride (126 mg, 1.10 mmol) was added to a solution of **13** (145 mg, 0.46 mmol) and triethylamine (120 mg, 1.20 mmol) in CH_2Cl_2 (4 ml), with stirring at 0 °C. After 15 min, the mixture was partitioned between AcOEt and a diluted aqueous solution of $NaHCO_3$. The organic layer was collected and dried. Removal of the solvent by evaporation under reduced pressure furnished **16** (180 mg, 100%) as a solid, which was used without further purification for the next reaction. An analytical sample of **16** was obtained as colorless crystals, mp 110—112 °C, by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{14}H_{17}Cl_2N_3O_4S$: C, 42.85; H, 4.35; Cl, 17.98; N, 10.66; S, 8.13. Found: C, 42.97; H, 4.39; Cl, 17.78; N, 10.51; S, 8.21. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.70 (3H, d, J=7 Hz), 2.9—3.4 (1H, m), 3.07 (3H, s), 4.22 (1H, dd, J=10, 5 Hz), 4.59 (1H, d, J=14.5 Hz), 4.71 (1H, dd, J=10, 7 Hz), 5.18 (1H, br), 5.51 (1H, d, J=14.5 Hz), 7.04 (1H, dd, J=8, 2 Hz), 7.27 (1H, d, J=2 Hz), 7.43 (1H, d, J=8 Hz), 7.73 (1H, s), 7.81 (1H, s).

(2*R,3*S**)-4-Azido-2-(2,4-dichlorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17)** A mixture of **16** (180 mg, 0.46 mmol), sodium azide (119 mg, 1.82 mmol) and DMF (3 ml) was stirred at 100 °C for 3 h. After being cooled, the mixture was partitioned between AcOEt and brine. The organic layer was dried and the solvent was distilled off under reduced pressure to leave an oil, which was chromatographed (5 g, AcOEt–hexane, 2 : 1, v/v) to give **17** (108 mg, 69%) as a solid. An analytical sample of **17** was obtained as colorless crystals, mp 116—117 °C, by recrystallization from benzene–hexane. *Anal.* Calcd for $C_{13}H_{14}Cl_2N_6O$: C, 45.76; H, 4.14; N, 24.63. Found: C, 45.81; H, 4.16; N, 24.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 2100. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.71 (3H, d, J=7 Hz), 2.6—3.2 (1H, m), 3.2—4.1 (2H, m), 4.59 (1H, d, J=14 Hz), 5.00 (1H, s), 5.50 (1H, d, J=14 Hz), 7.05 (1H, dd, J=8, 2 Hz), 7.28 (1H, d, J=2 Hz), 7.43 (1H, d, J=8 Hz), 7.74 (1H, s), 7.80 (1H, s).

(2*R,3*S**)-4-Amino-2-(2,4-dichlorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (18)** A solution of **17** (108 mg) in ethanol (4 ml) was shaken with 10% palladium–carbon (30 mg) under an H_2 atmosphere for 1 h. The catalyst was filtered off using Celite and the filtrate was concentrated under reduced pressure to give **18** (100 mg, 100%) as a solid, which was recrystallized from AcOEt–benzene to afford an analytical sample as colorless crystals, mp 154—156 °C. *Anal.* Calcd for $C_{13}H_{16}Cl_2N_4O$: C, 49.53; H, 5.12; N, 17.78. Found: C, 49.57; H, 5.02; N, 17.60. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.76 (3H, d, J=7 Hz), 2.5—3.5 (3H, m), 3.80 (3H, br s), 4.69 (1H, d, J=14.5 Hz), 5.24 (1H, d, J=14.5 Hz), 7.07 (1H, dd, J=8, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.60 (1H, d, J=8 Hz), 7.68 (1H, s), 8.09 (1H, s).

(2*R,3*S**)-2-(2,4-Dichlorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-4-[4-(trifluoromethyl)benzoylamino]-2-butanol (3a)** 4-(Trifluoromethyl)-benzoyl chloride (37 mg, 0.18 mmol) was added to a solution of **18** (46 mg, 0.15 mmol) in pyridine (1 ml), with stirring at 0 °C. After 30 min, a diluted aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with AcOEt. The extract was washed with brine and dried. The solvent was distilled off under reduced pressure to leave an oily residue, which was purified by column chromatography (3 g, AcOEt–hexane, 2 : 1, v/v) to give **3a** (53 mg, 75%) as a viscous oil. MS *m/z*: 489, 487 ($M^+ + 1$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1665, 1525. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.78 (3H, d, J=7 Hz), 2.7—3.2 (1H, m), 3.3—4.4 (2H, m), 4.69 (1H, d, J=14 Hz), 5.55 (1H, d, J=3 Hz), 5.64 (1H, d, J=14 Hz), 7.11 (1H, dd, J=8, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.53 (1H, d, J=8 Hz), 7.79 (1H, s), 7.92 (1H, s), 7.6—8.1 (4H, m).

Amide **3a** (53 mg) formed its oxalic acid salt (58 mg) as a colorless powder. mp 81 °C (dec.), on being mixed with 1 eq of oxalic acid in AcOEt–hexane.

(2*R,3*S**)-4-[(*E*)-4-Chlorocinnamoylamino]-2-(2,4-dichlorophenyl)-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (3b)** Following a procedure similar to that described for **3a**, **3b** was obtained as a viscous oil in 70% yield by treatment of **18** with (*E*)-4-chlorocinnamoyl chloride. MS *m/z*: 481, 479 ($M^+ + 1$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1665, 1620. ^{1}H-NMR (60 MHz, $CDCl_3$ + CD_3OD) δ: 0.87 (3H, d, J=7 Hz), 2.7—3.3 (1H, m), 4.82 (1H, d, J=14 Hz), 5.38 (1H, d, J=14 Hz), 6.46 (1H, d, J=16 Hz), 7.0—7.9 (8H, m), 7.73 (1H, s), 8.05 (1H, s).

Amide **3b** formed its oxalic acid salt as a colorless powder, mp 190—191 °C, on being mixed with 1 eq of oxalic acid in AcOEt–hexane.

(2*R,3*S**)-3-[(4-Chlorobenzoyl)amino]-2-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1a′)** Following a procedure similar to that described for the *threo* amide **1a**,[1] the *erythro* isomer **1a′** was obtained as a viscous oil by acylation of (2*R**,3*S**)-3-amino-2-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol[1] with 4-chlorobenzoyl chloride. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1655. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.45 (3H, d, J=6.5 Hz), 4.49 (1H, d, J=14 Hz), 5.23 (1H, dq, J=10, 6.5 Hz), 5.52 (1H, d, J=14 Hz), 5.71 (1H, br), 6.62 (1H, br d, J=10 Hz), 7.01 (1H, dd, J=8, 2 Hz), 7.30 (1H, d, J=2 Hz), 7.53 (1H, d, J=8 Hz), 7.79 (1H, s), 7.99 (1H, s).

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