HETEROCYCLES, Vol. 70, 2006, pp. 93 - 99. © The Japan Institute of Heterocyclic Chemistry.
Received, 21st August, 2006, Accepted, 22nd September, 2006, Published online, 26th September, 2006. COM-06-S(W)26

DIASTEREOSELECTIVE SYNTHESIS OF ATROPISOMERIC 3-(2-SUBSTITUTED ARYL)QUINAZOLIN-4-ONES AND THEIR STEREOCHEMICAL PROPERTIES[+]

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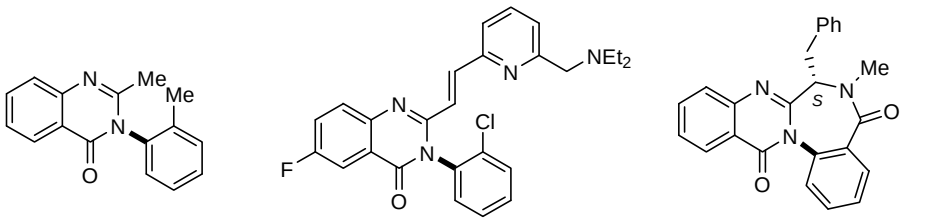
[+]*Dedicated to Professor S. M. Weinreb on the occasion of his 65th birthday*

Abstract – Atropisomeric {1-[(2-substituted aryl)-4-oxo-3,4-dihydro-quinazolin-2-yl]ethyl and -2-phenylethyl}carbamic acid *t*-butyl ester (**9a**–**c**) were diastereoselectively synthesized by acid-catalyzed cyclization of {2-[(2-substituted arylcarbamoyl)phenylimino]-1-methyl- and -1-benzyl-2-piperidin-1-yl}carbamic acid *t*-butyl ester (**8a**–**c**). Investigation of the stereochemical properties of **9** revealed that both atropisomers have high stereochemical stability and the (*aR*, S**)-form (**9R**[*]) is stereochemically more stable than the isomeric (*aS*, S**)-form (**9S**[*]).

INTRODUCTION

The 3-arylquinazolin-4-one nucleus is important and useful as a scaffold for biologically active molecules, as seen, *e.g.*, in methaqualone (an anticonvulsant) (**1**),[2] CP-465,022 (an AMPA receptor antagonist) (**2**),[3] and atropisomeric benzomalvin A & D (natural products with NK_1 receptor-antagonist activity) (**3**)[4] (Figure 1). The *o*-substitution at the 3-aryl moiety is also an important structural feature allowing the molecules to exhibit desirable biological activity, which endows the molecule with axial chirality to form separable atropisomers. It should be noted that the biological activity resides in only one of the atropisomers, *e.g.*, *aR* for **1**[2] and *aS* for **2**.[3] Thus, atropisomers and their stereoselective syntheses have attracted increasing attention.[5] Recently, one of the authors has reported a method using central chirality to induce new axial chirality in a stereoselective manner to synthesize tachykinin NK_1 antagonists.[6] This

communication deals with the atropisomeric 3-(2-substituted aryl)quinazolin-4-ones (**9**), *i.e.*, the atropdiastereoselective synthesis and stereochemical properties of the atropisomers (**9R*** and **9S***).



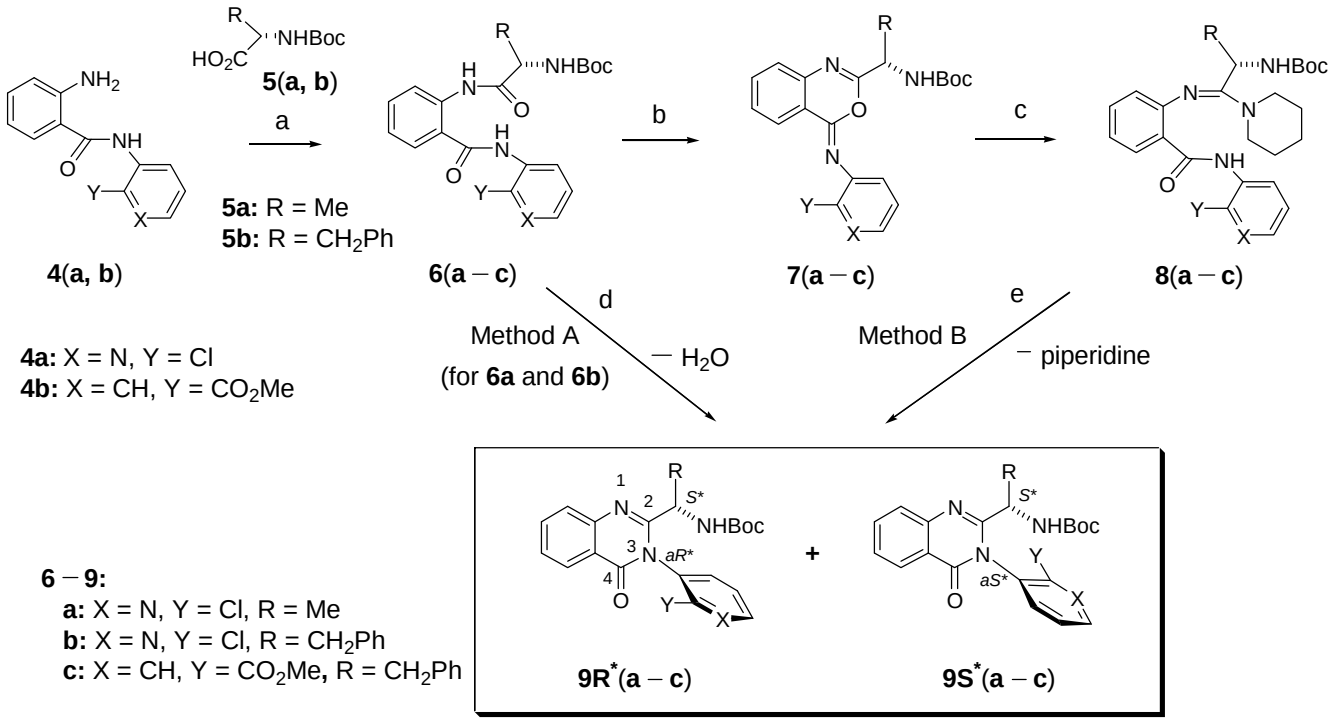
1: methaqualone **2**: CP-465,022 **3**: benzomalvin A & D

Figure 1. Representative biologically active molecules that possess the 3-arylquinazolin-4-one nucleus.

RESULTS AND DISCUSSION

The atropselective synthesis was examined for 3-(2-substitued aryl)quinazolin-4-ones (**9**), which possess an asymmetric center in the side chain at the 2-position originating from amino acids. The quinazolone nucleus was constructed by dehydrative cyclization of {1-[2-(2-substituted arylcarbamoyl)phenylcarbamoyl]-ethyl and -2-phenylethyl}-carbamic acid *t*-butyl ester (**6**) obtained from 2-amino-*N*-(2-chloropyridin-3-yl)benzamide (**4a**) and 2-amino-*N*-(2-methoxycarbonylphenyl)benzamide (**4b**) by conventional dehydro amidation with *N*-Boc amino acids [*N*-Boc-alanine (**5a**) and *N*-Boc-phenylalanine (**5b**)] (Scheme 1).[7] The dehydrative cyclization of **6** was performed using the following two methods, which we have recently reported for the synthesis of 2-ethoxycarbonyl-3-arylquinazolin-4-ones.[8] The first (method A) is dehydration of **6** with an excess of trimethylsilyl chloride (TMSCl) and Et_3N by heating in 1,2-dichloroethane. The second (method B) is dehydration of **6** *via* the amidine (**8**) under acidic conditions; the amidine **8** was prepared from **6** by treatment with I_2, PPh_3, and *i*-Pr_2NEt, followed by reaction of the product [iminobenzoxazine (**7**)] with piperidine.[9] The dehydrative cyclization of **6** and **8** afforded the diastereomers of **9**, *i.e.*, **R*** and **S*** (Scheme 1). The results of cyclization are summarized in Table 1.

Using method A, the compounds (**6a**) (X = N, Y = Cl, R = Me) and (**6b**) (X = N, Y = Cl, R = CH_2Ph) gave almost equal amounts of the diastereomers (**9R*** and **9S***) (Table 1, Entries 1 and 4). The diastereomers (**9R*****-a** and **9S*****-a**) were easily separated upon column chromatography, and the structure of the isomer (**9R*****-a**) was determined using single-crystal X-Ray analysis (see below). On the other hand, the diastereomers (**9R*****-b** and **9S*****-b**) showed the same Rf value on TLC and could not be separated by column chromatography. However, the single isomer (**9R*****-b**) was isolated by crystallization and the structure was determined in X-Ray analysis (see below). The structure of isomer (**9S*****-b**) was confirmed with ^{1}H-^{1}H COSY NMR using a mixture of **9R*****-b** and **9S*****-b**, although it was not obtained as a pure form.



Scheme 1. *Reagents and conditions*: (a) DCC, CH_2Cl_2, rt, 20 h, 93 % for **6a**, and 65 % for **6b**; (b) I_2, PPh_3, *i*-Pr_2NEt, CH_2Cl_2, r.t., 0.5 h, 68 % for **7a**, 88 % for **7b**, and 63 % for **7c** (from **4b**); (c) piperidine, EtOAc, rt, 15 h, quantitative yield for **8a**, **8b**, and **8c**; (d) TMSCl, Et_3N, $ClCH_2CH_2Cl$, 80 ºC (see Table 1); (e) acidic conditions (see Table 1 and reference 10).

Table 1. Formation of the atropisomeric 3-(2-substituted-aryl)quinazolin-4-ones (**9**) from **6** and **8**

Entry	Starting Compd.	Reaction Conditions				Product (**9**)				
		Reagent	Solvent	Temp.(℃)	Time (h)		Yield (%) [a]		Isomer Ratio [b]	Recovery of **6** (%)
							R*	**S***	**R***: **S***	
1	**6a**	TMSCl, Et_3N	$ClCH_2CH_2Cl$	80	28	**9a**	38	42	0.90 : 1	20
2	**8a**	$KHSO_4$	H_2O-dioxane	23	20	**9a**	58	14	4.1 : 1	
3	**8a**	SiO_2 [c]	$CHCl_3$	23	120	**9a**	49	43	1.2 : 1	
4	**6b**	TMSCl, Et_3N	$ClCH_2CH_2Cl$	80	120	**9b**	(70)		0.94 : 1	18
5	**8b**	$KHSO_4$	H_2O-dioxane	23	27	**9b**	(95)		2.5 : 1	
6	**8b**	AcOH	THF	23	27	**9b**	(100)		2.0 : 1	
7	**8b**	SiO_2 [c]	$CHCl_3$	23	120	**9b**	(100) [d]		9.0 : 1	
8	**8c**	SiO_2 [c]	$CHCl_3$	28	27	**9c**	(95) [e]		3.5 : 1	

[a] Isolated yield for **9a**, and yield of the the diastereomeric mixture of **9b** and **9c** in parentheses. [b] Ratio determined from the isolated isomer for **9a**, and ratio estimated from the ^{1}H NMR spectrum of the diastereomeric mixture for **9b** and **9c**. [c] Merck silica gel 60 for column chromatography (large excess was used). [d] **9R*-b** was isolated as colorless crystals in 77 % yield. [e] **9R*-c** was isolated as colorless crystals in 50 % yield.

Using method B,[10] the cyclization of the amidine (**8a**–**c**) proceeded under mild conditions (at room temperature in the presence of excess acid, *e.g.*, aq. $KHSO_4$, AcOH, and silica gel) to obtain the product (**9R*** and **9S***) in good yields. Although the ratio differed depending on the substrate and the reaction conditions, cyclization generally occurred atropdiastereoselectively to yield the single isomer (**9R*****a**–**c**) in preference to the diastereomer (**9S*****a**–**c**) (Table 1, Entries 2, 3, and 5–8). Especially high stereoselectivity was observed in the cyclization of **8a** in aqueous dioxane with $KHSO_4$ to give **9R*****-a** and **9S*-a**, in 58 % and 14 % isolated yield, respectively (Table 1, Entry 2). Also the cyclization of **8b** and **8c** in $CHCl_3$ with silica gel (Table 1, Entries 7 and 8) afforded **9R*****-b** and **9R*****-c**[11] in preference to the **9S*** isomers, in the ratio of 9.0 : 1 and 3.5 : 1, respectively. Taking into the consideration the fact that the isomer (**9R***) is thermodynamically more stable than the isomer (**9S***), as described below, the stereoselectivity may be explained by the difference in the thermodynamic stability of the intermediates for cyclization, of which the stereochemistry and stability difference are presumably similar to that of the products.

The stereochemistry of the atropisomer (**9R*****a**–**c**) was determined using X-Ray structural analysis. The ORTEP drawings are shown in Figure 2. All **9R***(**a**–**c**) have similar conformations regardless of the substituent difference. As expected, the *N*-aryl ring occurs perpendicular to the quinazolone ring. It is interesting to note that the relative spatial orientation of the bulky NHBoc group and the 2-substituent in the aryl ring are disposed in opposite directions, with the proton at the asymmetric carbon above the plane of the aryl nucleus. Thus, the relative stereochemistry between the axial and central chirality of **9R*** was shown to be (*aR**, *S**), which presumably is sterically less hindered and consequently more stable than the diastereomer (**9S***) [*i.e.*, (*aS**, *S**)].

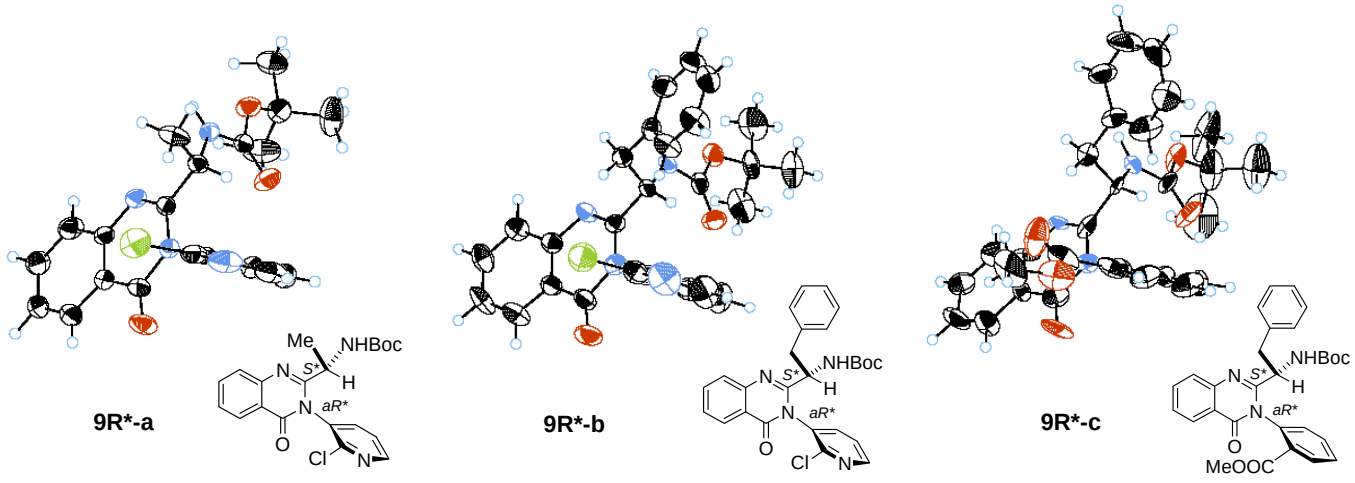
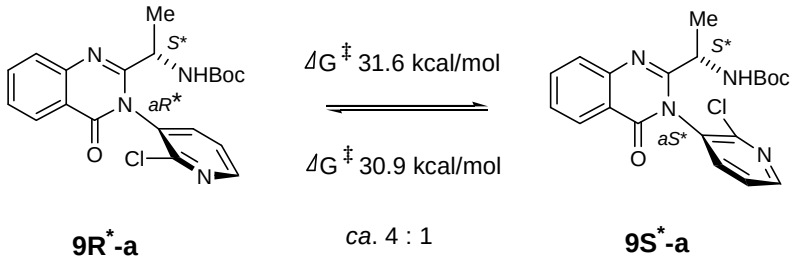


Figure 2. ORTEP drawings of **9R*****-a**, **9R*****-b**, and **9R*****-c**.

Since the 3-(2-substituted)aryl group of **9R*** and **9S*** occurs at the position wedged between two substituents (at 2- and 4-positions) of the quinazoline ring and thus the rotation around the axis is highly

restricted, the atropisomers (**9R*** and **9S***) are assumed to have high stereochemical stability. It was found that the atropisomers (**9R*****-a** and **9S*****-a**) did not interconvert in $CDCl_3$ at room temperature after 2 weeks. The interconversion between **9R*****-a** and **9S*****-a** was examined at 108 °C in DMSO-d_6; the ratio from each isomer was determined using ^{1}H NMR. The conversion was found to be extremely slow; *e.g.*, the diastereomeric excess after 6-h and 12-h storage of the solution at 108 °C was 75 % (**9R*****-a** : **9S*****-a** = 1 : 0.14) and 60 % (the ratio = 1 : 0.25), respectively, for **9R*****-a**, and 64 % (**9S*****-a** : **9R*****-a** = 1 : 0.22) and 27 % (the ratio = 1 : 0.57), respectively, for **9S*****-a**. The conversion from **9R*****-a** to **9S*****-a** reached equilibrium of a *ca*. 4 : 1 ratio in 11 h. From the experimental data, the activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) from **9R*****-a** to **9S*****-a** was calculated[12] to be *ca*. 31.6 kcal/mol (132 kJ) and that from **9S*****-a** to **9R*****-a** to be *ca*. 30.9 kcal/mol (129 kJ), which also indicates that **9R*****-a** (*aR**, *S**) is more stable than **9S*****-a** (*aS**, *S**).



9R***-a** **9S*****-a**

Scheme 2. Interconversion between **9R*****-a** and **9S*****-a**.

In conclusion, the atropisomeric 3-(2-substituted aryl)quinazolin-4-ones (**9**) were diastereoselectively synthesized[11] *via* the amidine (**8**), which bears a chiral center from amino acids. The stereochemical properties of the atropisomers (**9R*** and **9S***) were examined using X-Ray analysis and temperature-dependent interconversion experiment to reveal that the (*aR**, *S**) form is more stable than the isomeric (*aS**, *S**) form. The compounds (**9**) prepared in this investigation would be useful intermediates for a variety of biologically active compounds, and further study on their scope and limitations is in progress. The stereoselectivity and stereochemical properties of the atropisomers described here yield valuable information on the chemistry of atropisomers.

ACKNOWLEDGMENT

Continuous support by Takeda Pharmaceutical Company, Ltd. is gratefully acknowledged.

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10. Representative procedures for the dehydrative cyclization of **8** to **9** (method B): (a) A mixture of the amidine (**8a**), which was prepared from the iminobenzoxazine (**7a**) (1.70 g) and piperidine (4.20 mL) in EtOAc (150 mL), 1,4-dioxane (80 mL), and 0.2 M aq. $KHSO_4$ (80 mL) was stirred at rt overnight. The organic layer was diluted with EtOAc, and the mixture was washed with H_2O, dried over Na_2SO_4, and concentrated. Purification of the residue on flash chromatography (Fuji Silysia silica gel BW300, 30→50% EtOAc/hexane) gave **9R*-a** (0.99 g, 58 %) and **9S*-a** (0.24 g, 14 %). Selected data for **9R*-a**: colorless crystals; mp 199–200 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (m, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.82 (m, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.56–7.47 (m, 2H), 5.45 (m, 1H), 4.38 (m, 1H), 1.50–1.30 (m, 12H); ^{1}H NMR (DMSO-d_6) δ 8.59 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 8.4

Hz, 1H), 8.06 (d, *J* = 13.6 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 14.0 Hz, 1H), 7.70 (dd, *J* = 7.2, 4.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 4.13 (m, 1H), 1.39–1.05 (m, 12H); Selected data for **9S*-a**: colorless crystals; mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (d, *J* = 4.0 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 7.84 (m, 1H), 7.79–7.72 (m, 2H), 7.57–7.45 (m, 2H), 5.58 (m, 1H), 4.43 (m, 1H), 1.49–1.31 (m, 12H); ^{1}H NMR (DMSO-d_6) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 4.38 (m, 1H), 1.39-1.19 (m, 12H).

(b) A mixture of the amidine (**8b**) (0.56 g), silica gel 60 (Merck) (12 g), and $CHCl_3$ (56 mL) was stirred at rt for 5 days. Conventional work-up gave a mixture of **9R*-b** and **9S*-b** (0.48 g) (the ratio = 9.0:1 from ^{1}H NMR) as a white solid, from which **9R*-b** was isolated as colorless crystals (0.37 g, 77 %). Selected data for **9R*-b**: mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 8.61 (d, *J* = 3.6 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.93–7.70 (m, 3H), 7.59–7.46 (m, 2H), 7.24–7.12 (m, 3H), 6.95 (d, *J* = 6.4 Hz, 2H), 5.21 (d, *J* = 9.2 Hz, 1H), 4.55–4.45 (m, 1H), 3.24 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.87 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.31 (s, 9H). Selected data for **9S*-b**: diagnostic signals in the ^{1}H NMR ($CDCl_3$) are as follows: δ 8.46 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 6.6 Hz, 1H), 7.14 (dd, *J* = 4.8, 7.8 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 5.50 (d, *J* = 9.0 Hz, 1H), 4.54–4.45 (m, 1H), 3.31 (dd, *J* = 13.0, 9.6 Hz, 1H), 3.06 (dd, *J* = 13.0, 4.8 Hz, 1H), 1.41 (s, 9H).

Similarly, the amidine (**8c**) gave **9R*-c** and **9S*-c**. Selected data for **9R*-c**: mp 181–182 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.3 Hz, 2H), 7.78 (m, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.58–7.50 (m, 2H), 7.14 (m, 3H), 6.85 (d, *J* = 6.6 Hz, 2H), 5.7–5.3 (broad, 1x0.8H), 5.11 (broad, 1x0.2H), 4.72 (ddd, 12.6, 4.8, 4.3 Hz, 1x0.8H), 4.56 (broad, 1x0.2H), 3.64 (s, 3H), 3.08 (dd, *J* = 13.8, 4.3 Hz, 1H), 2.83 (broad, 1H), 1.34 (s, 9x0.8H), 1.01 (s, 9x0.2H). Selected data for **9S*-c**[11]: diagnostic signals in the ^{1}H NMR ($CDCl_3$) are as follows: 7.57 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 4.51 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.68 (s, 3H), 3.25 (dd, *J* = 19.2, 8.4 Hz, 1H), 2.95 (broad, 1H), 1.33 (s, 9x0.8H), 1.07 (s, 9x0.2H).

11. The diastereomers (**9R*-c** and **9S*-c**) showed the same Rf value on TLC and could not be separated by column chromatography. The single isomer (**9R*-c**) was isolated by crystallization and the structure was determined in X-Ray analysis (Figure 2). The structure of isomer (**9S*-c**) was confirmed with ^{1}H-^{1}H COSY NMR using a mixture of **9R*-c** and **9S*-c**.
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