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Versatile synthesis of quaternary 1,3-oxazolidine-2,4-diones and their use in the preparation of α-hydroxyamides

Omar Merino, Blanca M. Santoyo, Luisa E. Montiel, Hugo A. Jiménez-Vázquez, L. Gerardo Zepeda, Joaquín Tamariz *

Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., Mexico

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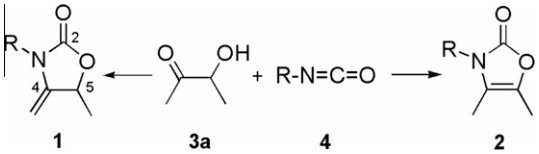
ABSTRACT

A new approach to the synthesis of 1,3-oxazolidine-2,4-diones, via a two-step reaction sequence, starting from the readily available α-ketols and isocyanates, is reported. The condensation of the latter led to the key precursors 4-methylene-2-oxazolidinones, which are converted into the diones by an oxidative cleavage of the exocyclic double bond. Thus, 5,5-disubstituted 1,3-oxazolidine-2,4-diones can be accessed in good yields from the appropriate functionalized α-ketols. Moreover, two alternative routes are also described either by functionalization of 4-oxazolin-2-ones or by alkylation of the 1,3-oxazolidine-2,4-dione core previously prepared. Upon hydrolysis of the 1,3-oxazolidine-2,4-diones, a series of α-hydroxyamides bearing a quaternary stereocenter were obtained.

1,3-Oxazolidine-2,4-diones are compounds having a chemically attractive and versatile heterocyclic scaffold, which is found in a variety of pharmacological active compounds[1] exhibiting antidiabetic,[2] anticonvulsant,[3] and aldose reductase inhibitory activities,[4] as well as fungicidal and herbicidal action.[5] The more common methods for the preparation of these heterocycles involve the ring formation process from α-hydroxyesters or α-hydroxyamides by treatment with a reagent already carrying the carbonyl function, such as ureas, dialkyl carbonates, isocyanates, carbodiimides, or phosgene.[2,6,7] Certainly, the opposite procedure, hydrolysis of 1,3-oxazolidine-2,4-diones, can lead to α-hydroxyamides,[8] which are important templates for the construction of complex molecules[9] or precursors of the biologically seminal α-hydroxyacids,[10] and found as subunits in natural products.[11] Therefore, the development of alternative and efficient methods, starting from diverse substrates[8,12] that allow access to 1,3-oxazolidine-2,4-diones, and from these to α-hydroxyamides appears to be highly desirable.

Despite the profound interest regarding the medicinal and synthetic potential of 2-oxazolidinones, as chiral auxiliaries, versatile intermediates, biologically active compounds, and β-amino alcohol precursors,[13] 4-oxazolin-2-ones and 4-methylene-2-oxazolidinones have received little attention as useful synthons.[14] However, an intense effort devoted to the preparation of these heterocycles has recently manifested itself in the literature.[12d,15] In this sense, we have designed a regioselective synthesis of N-substituted 4-methylene-2-oxazolidinones **1** and 4-oxazolin-2-ones **2**, starting from α-ketol **3a** and a series of isocyanates **4** (Scheme 1).[16] An alternative one-pot synthesis of 4-oxazolin-2-ones **2**, consisting of a cascade condensation of **3a** with **4**, under thermal or microwave (MW) irradiation as well and solvent-free conditions was recently reported, as was the use of these compounds in the construction of complex fused heterocyclic systems.[17] In this Letter, we describe a protocol for the efficient conversion of substituted 4-methylene-2-oxazolidinones **1** into 1,3-oxazolidine-2,4-diones **6**, as well as the functionalization of the latter for the synthesis of α-hydroxyamides.

The precursors 4-methylene-1,3-oxazolidinones **5a–d** were prepared in high yields (86–93%) by heating (130 °C, 24 h) a solvent-free mixture of α-ketol **3b** and isocyanates **4a–d** (Scheme 2) (Table 1).[18] The key step for the conversion of 1,3-oxazolidinones



Scheme 1.

* Corresponding author. Fax: +52 55 5586 6621.
E-mail addresses: jtamarizm@gmail.com, jtamariz@woodward.encb.ipn.mx (J. Tamariz).

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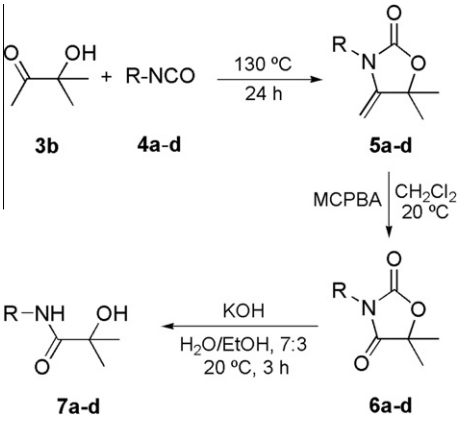


Scheme 2.

Table 1
Yields of compounds **5a–d**, obtained by condensation of α-ketol **3b** and isocyanates **4a–d**[a]

Entry	**4** (*R*)	**5**[b] (%)
1	**4a** (C_6H_5)	**5a** (86)
2	**4b** (C_6H_4-4-OMe)	**5b** (93)
3	**4c** (C_6H_4-3-OMe)	**5c** (83)
4	**4d** (C_6H_4-4-Cl)	**5d** (88)

[a] Carried out at 130 °C, no solvent, for 24 h.
[b] After purification by column chromatography and recrystallization.

5a–d into 5,5-dimethyl-1,3-oxazolidine-2,4-diones **6a–d** was carried out by oxidative cleavage of the exocyclic double bond of the 4-methylene-1,3-oxazolidinones **5a–d** with *m*-chloroperbenzoic acid (MCPBA) under mild conditions (Scheme 2). We have described this methodology for the preparation of N-substituted 5-alkylidene-1,3-oxazolidine-2,4-diones from novel exocyclic dienes, albeit in low to modest yields.[19] Unlike the latter procedure, in which only 1.5 mol equiv of MCPBA were used, the yield of diones **6a–d** was significantly improved when an excess of the oxidant reagent was added to the reaction mixture (Table 2, entries 1–3). This supports the idea that more than one mol equiv of MCPBA is involved in such cleavage.[20]

Upon hydrolysis of the series of 1,3-oxazolidine-2,4-diones **6a–d** under alkaline conditions, α-hydroxyamides **7a–d** were obtained in moderate to good yields (47–90%). The series of compounds **6** and **7** were characterized by spectrometric analysis. Oxazolidine-2,4-diones **6a** and **6d**, and α-hydroxyamide **7a** were obtained as crystals and their structures were also established by X-ray diffraction (Figs. 1 and 2).[21] It is noteworthy that in both structures of diones (Fig. 1 shows only that of **6d**) the heterocycle is planar, maintaining the nitrogen atom coplanar to the carbonyl groups, because of its sp^2-like hybridization. The conformation of the aryl ring is in a quasi-orthogonal orientation with respect to the heterocycle, as observed for analogous compounds.[16,17,19] In the case of

Table 2
Yields of compounds **6a–d**, obtained by oxidative cleavage of **5a–d** with MCPBA[a]

Entry	**5** (*R*)	MCPBA (mol equiv)	*t* (h)	**6**[b] (%)
1	**5a** (C_6H_5)	2	36	**6a** (56)
2	**5a** (C_6H_5)	3	30	**6a** (70)
3	**5a** (C_6H_5)	4	24	**6a** (92)
4	**5b** (C_6H_4-4-OMe)	4	24	**6b** (95)
5	**5c** (C_6H_4-3-OMe)	4	24	**6c** (92)
6	**5d** (C_6H_4-4-Cl)	4	24	**6d** (97)

[a] Carried out at 20 °C, CH_2Cl_2 as solvent.
[b] After purification by column chromatography.

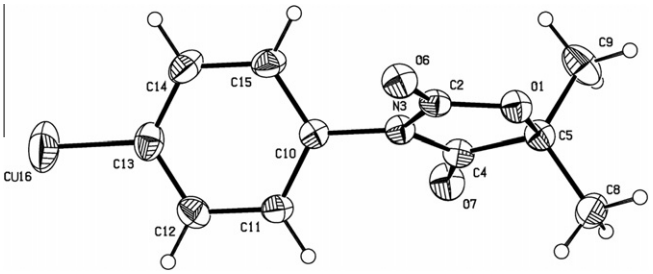


Figure 1. Molecular structure of **6d** (ellipsoids with 30% probability level).

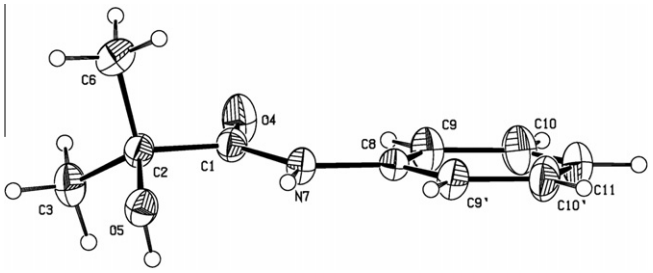
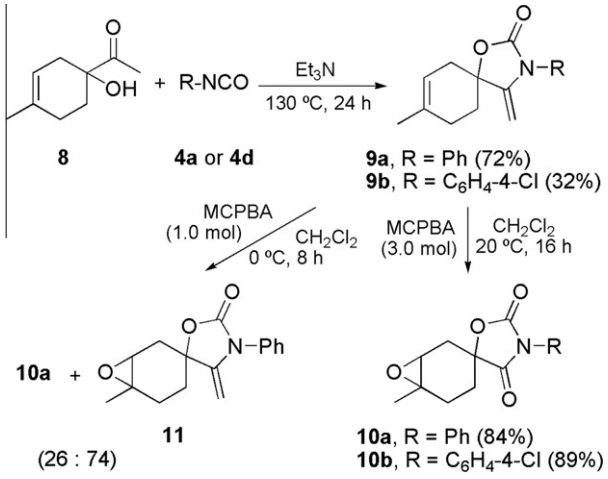


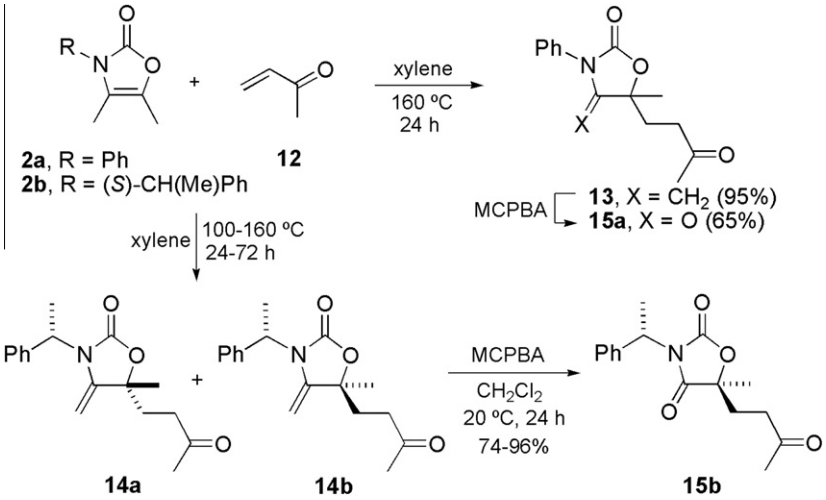
Figure 2. Molecular structure of **7a** (ellipsoids with 30% probability level).

7a, however, the amide moiety, including the phenyl ring, keeps a planar conformation in the crystalline state (Fig. 2), probably due to the detected intramolecular hydrogen bonding between the N–H proton and the oxygen of the hydroxyl group (2.23 Å). The crystal lattice also shows an intermolecular hydrogen bonding between the O–H proton and the oxygen atom of the carbonyl group of another molecule.

Owing to the successful preparation of 1,3-oxazoline-2,4-diones **6a–d** by oxidative cleavage of **5a–d**, we extended the same procedure to the case of α-ketol **8**, which can be readily obtained.[22] Thus, by reacting the latter with isocyanates **4a** or **4d** in the presence of triethylamine, the spiro-compounds **9a–b** were prepared, respectively (Scheme 3). Treatment of these compounds with 3.0 mol equiv of MCPBA gave rise not only to the desired oxidative cleavage of the exocyclic double bond, but also to the epoxidation of the endocyclic double bond to afford spiro-compounds **10a–b** in good yields. Interestingly, each product was obtained as inseparable stereoisomeric mixtures in high ratios (>90:<10), as shown by the ^{1}H NMR spectra of the crudes. In order to evaluate the reactivity between the exocyclic and endocyclic double bonds with the



Scheme 3.



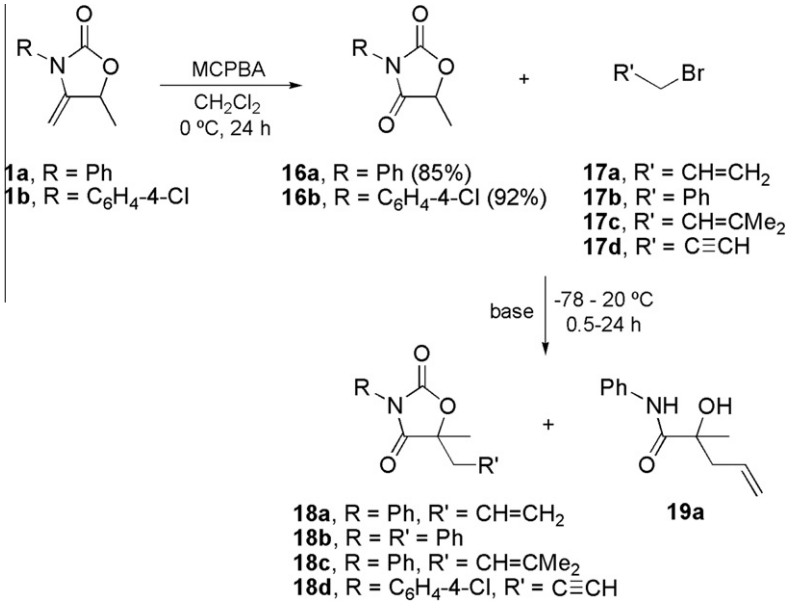
Scheme 4.

oxidation reagent, the reaction was carried out with a lesser amount (1.0 mol equiv) of MCPBA and at lower temperature (0 °C). After stirring for 8 h, the reaction led to a mixture of **10a** and epoxide **11** in a ratio of 26:74, respectively. Albeit the mixture was obtained in low yield (12%; the rest was starting material), this result indicates that the endocyclic double bond reacted faster than the exocyclic one.

We also investigated the versatility of this methodology in the synthesis of the non-symmetrically 5,5-disubstituted 4-methylene-1,3-oxazolidinones **13** and **14** (Scheme 4). Compound **13** was synthesized in 95% yield by a thermally-promoted conjugate addition of 4-oxazolin-2-one **2a** to methyl vinyl ketone (**12**), as previously reported.[16,17] In the case of the chiral derivatives **14**, their preparation was carried out by addition of the chiral 4-oxazolin-2-one **2b** to **12** at 160 °C for 24 h, to give a mixture of diastereoisomers **14a** and **14b** in a ratio of 29:71.[23] The diastereoselectivity was significantly improved when the reaction was carried out at a lower temperature (100 °C) for a longer reaction time (72 h), leading to a mixture of **14a**/**14b** (9:91) (Scheme 4). 4-Oxazolin-2-one **2b** was readily obtained by condensation of **3a** with chiral isocyanate **4e** (R = (*S*)-CH(Me)Ph), at 120 °C for 24 h, in 75% yield.

When derivatives **13** and **14b** were treated with an excess (3.0 mol equiv) of MCPBA at room temperature for 24 h, 1,3-oxazolidine-2,4-diones **15a**–**b** were obtained in good yields (65–74%) (Scheme 4). The yield of the enantiopure dione **15b** was significantly improved (96%) when a large excess (6.0 mol equiv) of the oxidant was added. It was interesting that no products coming from a possible Baeyer–Villiger rearrangement on the side-chain methyl ketone moiety were observed. This high chemoselectivity, in contrast with spiro-compounds **9**, could be due to the higher reactivity of the exocyclic double bond of the enamide moiety.

An alternative approach to the preparation of C-5 quaternary 1,3-oxazolidine-2,4-diones could be designed on the basis of the alkylation of mono-substituted 1,3-oxazolidine-2,4-diones, **16a**–**b** (Scheme 5).[8b,24] The latter were obtained from the previously reported precursors **1a**–**b**,[16,17] by treatment with MCPBA (4.0 mol equiv) in methylene chloride at 0 °C for 24 h, providing 1,3-oxazolidine-2,4-diones **16a**–**b** in good yields (85–92%). The



Scheme 5.

Table 3
Results of the alkylation of oxazolidine-2,4-dione **16a**–**b** with different electrophiles[a]

Entry	16	17	Base	T (°C)	t (h)	18/19[b] (%)
1	**16a**	**17a**	LDA	−78	1	**18a** (45)
2	**16a**	**17a**	LHMDS	−78	0.5	**18a** (80)/**19a** (15)
3	**16a**	**17b**	LDA	20	24	**18b** (40)
4	**16a**	**17b**	LHMDS	20	24	**18b** (20)
5	**16a**	**17c**	LDA	20	24	**18c** (0)
6	**16a**	**17c**	LHMDS	−78	1	**18c** (69)
7	**16b**	**17d**	LHMDS	−78	0.5	**18d** (83)

[a] Deprotonation of **16a**–**b** was carried out in THF as the solvent, under N_2 atm, at −78 °C, and addition of the electrophile at −78 °C. Then, the reaction mixture was maintained at the indicated temperature and reaction.
[b] After purification by column chromatography.

structure of **16a** was established by spectroscopy and X-ray crystallography,[21] showing similar structural features as for **6a** and **6d**.

Alkylation of **16a** was firstly carried out with lithium diisopropylamide (LDA) in THF at −78 °C, using allyl bromide (**17a**) as the electrophile, to afford 1,3-oxazolidine-2,4-dione **18a** as an oil in moderate yield (45%) (Table 3, entry 1). In contrast, when **16a** was deprotonated with lithium hexamethyldisilazide (LHMDS), the yield was drastically improved and the reaction time was shortened, to give a mixture of **18a** and α-hydroxyamide **19a** in 80% and 15% yields, respectively (Table 3, entry 2). However, when the electrophile was benzyl bromide (**17b**), the reaction was more efficient with LDA under analogous conditions, to furnish **18b** in a modest yield (40%), since by using LHMDS only a low yield was observed (20%) (Table 3, entries 3 and 4). An opposite outcome was obtained with prenyl bromide (**17c**), leading to 1,3-oxazolidine-2,4-dione **18c** in 69% yield when the reaction was promoted with LHMDS. In contrast, the starting material was recovered exclusively when LDA was used (Table 3, entries 5 and 6). Compound **18b** was obtained as crystals and its structure was established by spectroscopy and single crystal X-ray diffraction (Fig. 3).[21] The X-ray structure shows planarity of the heterocycle and is almost perpendicular to the *N*-benzene ring, as for **6a**, **6d**, and **16a**. When this method of alkylation was applied to the reaction between dione **16b** and propargyl bromide (**17d**), in the presence of LHMDS at low temperature for 0.5 h, derivative **18d** was obtained in good yield (83%).

In summary, we have developed a new approach to the synthesis of 1,3-oxazolidine-2,4-diones **6a**–**d**, through an oxidative cleavage with MCPBA of their corresponding 4-methylene 1,3-oxazolidin-2-ones **5a**–**d**. Upon alkaline hydrolysis of the latter, the series of α-hydroxyamides **7a**–**d** bearing a quaternary stereocenter were obtained. This stereocenter was introduced in the dione frame of **15a** by functionalization of 4-oxazolin-2-one **2a** via conjugate addition to a Michael acceptor, such as **12**, followed by the oxidative cleavage of **13**. This methodology was also efficient in its chiral version for the asymmetric preparation of the enantiopure derivative **15b**. Alkylation of the 1,3-oxazolidine-2,4-dione core of **16a**–**b** with diverse electrophiles was an alternative route to yield quaternary 1,3-oxazolidine-2,4-diones **18a**–**d**. Construction of 1,3-oxazolidine-2,4-diones embedded in a spiro-structure was also possible starting from α-ketol **8**, which was transformed into the desired derivatives **10a**–**b**.

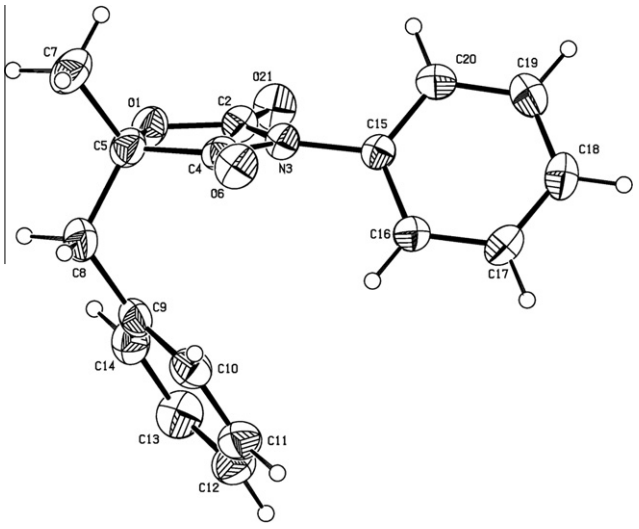


Figure 3. Molecular structure of **18b** (ellipsoids with 30% probability level).

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18. *Typical experimental procedures: Preparation of* **5d**: A mixture of **3b** (0.10 g, 0.98 mmol) and **4d** (0.18 g, 1.18 mmol) was placed in a threaded ACE glass pressure tube with a sealed Teflon screw cap under N_2. The mixture was stirred and heated at 130 °C for 24 h. The mixture was diluted with CH_2Cl_2 (10 mL) and filtered, then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (30 g per gram of crude, hexane/EtOAc, 9:1) to give **5d** (0.20 g, 88%) as colorless crystals. R_f = 0.65 (hexane/EtOAc, 7:3). Mp 127–129 °C. IR (film): $\bar{\nu}$ 1764, 1681, 1639, 1499, 1407, 1303, 1189, 1089, 1078, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 6H, 2CH_3C-5), 4.07 (d, J = 2.9 Hz, 1H, CH_2=), 4.14 (d, J = 2.9 Hz, 1H, CH_2=), 7.27–7.33 (m, 2H, H-Ar), 7.43–7.48 (m, 2H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0 (2CH_3C-5), 81.4 (CH_2=), 82.6 (C-5), 128.3 (2H-Ar), 129.8 (2H-Ar), 132.5 (Ar), 134.0 (Ar), 151.4 (C-4), 154.2 (C-2); MS (70 eV): m/z 239 (M^++2, 17), 237 (M^+, 56), 192 (36), 178 (82), 158 (67), 138 (100), 111 (45), 75 (41), 56 (71). HRMS (EI): calcd for $C_{12}H_{12}ClNO_2$ $[M]^+$ 237.0557; found 237.0562.
Preparation of **6d**: A mixture of **5d** (0.10 g, 0.42 mmol) and MCPBA (0.146 g, 0.84 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 12 h. Then, at the same temperature, MCPBA (0.146 g, 0.84 mmol) was added and the mixture stirred for 12 h. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with an aqueous saturated solution of $NaHCO_3$ until neutral. The organic layer was dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (30 g per gram of crude, hexane/EtOAc, 9:1) to give **6d** (0.098 g, 97%) as colorless crystals. R_f = 0.68 (hexane/EtOAc, 7:3). Mp 118–119.5 °C. IR (film): $\bar{\nu}$ 1820, 1743, 1500, 1421, 1283, 1239, 1177, 1091, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.68 (s, 6H, 2CH_3C-5), 7.38–7.48 (m, 4H, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7 (2CH_3C-5), 83.5 (C-5), 126.6 (2H-Ar), 129.3 (2H-Ar), 129.4 (Ar), 134.5 (Ar), 152.8 (C-2), 174.5 (C-4); MS (70 eV): m/z 239 (M^+, 9), 169 (24), 167 (61), 152 (100), 125 (17), 90 (34), 69 (21), 63 (21). HRMS (EI): calcd for $C_{11}H_{10}ClNO_3$ $[M]^+$ 239.0349; found 239.0352.
Preparation of **7d**: A mixture of **6d** (0.10 g, 0.42 mmol) and KOH (0.094 g, 1.68 mmol) in a mixture of EtOH/H_2O (3:7) (10 mL) was stirred at room temperature for 3 h. The solvent was removed under vacuum, and the residue was dissolved with CH_2Cl_2 (10 mL) and washed with a 5% aqueous solution of HCl until neutral. The organic layer was dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (30 g per gram of crude, hexane/EtOAc, 9:1) to give **7d** (0.098 g, 47%) as a yellow powder. R_f = 0.36 (hexane/EtOAc, 7:3). Mp 98–100 °C. IR (film): $\bar{\nu}$ 3388, 3298, 1737, 1666, 1592, 1533, 1496, 1398, 1378, 1141, 1089, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 6H, 2CH_3C-5), 2.76 (br s, 1H, OH), 7.25–7.32 (m, 2H, H-Ar), 7.50–7.56 (m, 2H, H-Ar), 8.72 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9 (2CH_3C-2), 74.3 (C-2), 120.8 (2H-Ar), 129.0 (2H-Ar), 129.3 (Ar), 136.1 (Ar), 174.2 (C-1); MS (70 eV): m/z 215 (M^++2, 26), 213 (M^+, 80), 155 (31), 129 (33), 127 (100), 99 (7), 59 (57). HRMS (EI): calcd for $C_{10}H_{12}ClNO_2$ $[M]^+$ 213.0557; found 213.0567.
Preparation of **18c**: To a solution of **16a** (0.10 g, 0.523 mmol) in dry THF (3 mL), under N_2 atmosphere and at -78 °C, LHMDS (0.105 g, 0.628 mmol) was slowly added and stirred for 1 h. Then, at the same temperature, **17c** (0.094 g, 0.628 mmol) in dry THF (2 mL), was added dropwise and the mixture was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL), and the organic layer was washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL) until neutral. The organic layer was dried (Na_2SO_4), and the solvent removed under vacuum. The residue was purified by column chromatography on silica gel (30 g per gram of crude, hexane/EtOAc, 98:2) to give **18c** (0.094 g, 69%) as a white powder. R_f = 0.70 (hexane/EtOAc, 7:3). Mp 74–75 °C. IR (film): $\bar{\nu}$ 1814, 1746, 1502, 1402, 1172, 767 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3C-5), 1.68 (d, J = 1.0 Hz, 3H, CH_3C=), 1.74 (d, J = 1.0 Hz, 3H, CH_3C=), 2.63 (br dd, J = 14.5, 7.5 Hz, 1H, CH_2CH=), 2.69 (br dd, J = 14.5, 8.0 Hz, 1H, CH_2CH=), 5.12–5.17 (m, 1H, CH=), 7.33–7.36 (m, 2H, H-Ar), 7.39–7.43 (m, 1H, H-Ar), 7.46–7.51 (m, 2H, H-Ar); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.1 (CH_3CH=), 22.0 (CH_3C-5), 25.9 (CH_3CH=), 35.9 (CH_2CH=), 86.3 (C-5), 114.5 (CH=), 125.6 (2H-Ar), 128.8 (H-Ar), 129.3 (2H-Ar), 131.0 (Ar), 139.4 (Me_2C=), 153.6 (C-2), 174.4 (C-4). HRMS (FAB): calcd for $C_{15}H_{17}NO_3$ $[M+1]^+$ 260.1287; found 260.1290.
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21. CCDC-743102 (for **6a**), -743103 (for **6d**), -743104 (for **7a**), -743105 (for **16a**), and -743106 (for **18b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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