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Synthesis of 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines and 2-(3-hydroxybutyl)-1-pyrroline using α-lithiated 2-methyl-1-pyrroline

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ABSTRACT

Condensation of 2-methyl-1-pyrroline with chloroacetone or 3-chloro-2-butanone using LDA in THF afforded novel 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines via a peculiar reaction mechanism instead of the anticipated 2-(3-oxobutyl)-1-pyrrolines. The intermediacy of 2-(2,3-epoxy-2-methylalkyl)-1-pyrrolines in the latter transformation was demonstrated by immediate reductive epoxide ring opening utilizing lithium aluminium hydride in diethyl ether. Furthermore, 2-(3-oxobutyl)-1-pyrroline was prepared via an alternative approach through alkylation of 2-methyl-1-pyrroline with 3-chloro-2-(methoxymethyloxy)-1-propene using LDA in THF, followed by acid hydrolysis. Reduction of 2-(3-oxo butyl)-1-pyrroline by sodium borohydride in methanol afforded the corresponding 2-(3-hydroxybutyl)-1-pyrroline in good yield.

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1. Introduction

For many years, the pyrrolidine scaffold has attracted both synthetic and medicinal chemists due to its wide applicability, resulting in the synthesis of a large variety of bioactive pyrrolidine derivatives.[1] On the other hand, the closely related 1-pyrroline motif has received considerably less attention in the literature. Whereas, for example, the class of 2-(hydroxyalkyl)pyrrolidines has been evaluated rather extensively,[2] only few reports are available regarding the synthesis and utility of 2-(hydroxyalkyl)-1-pyrrolines. In that respect, 2-(2-carbamoyl-2-hydroxyethyl)-1-pyrrolines have been reported as potential bactericides,[3] 2-(3-hydroxyalkyl)-1-pyrrolines have been applied as synthons for the preparation of pyrrolizidine derivatives[4] and 2-(4-hydroxyalkyl)-1-pyrrolines have been used as precursors for the synthesis of (−)-slaframine,[5] (−)-swainsonine[6] and (+)-cylindricine C.[7]

From a synthetic point of view, 2-(2-hydroxyalkyl)-1-pyrrolines can be easily obtained via the addition of α-lithiated 2-methyl-1-pyrroline onto carbonyl compounds, which has been demonstrated by the synthesis of a range of representatives.[8] Indeed, functionalization of 2-methyl-1-pyrroline via nucleophilic substitution or addition reactions of the corresponding 1-azaallylic anion constitutes a useful methodology for the preparation of a variety of azaheterocyclic systems.[8,9] If, however, the synthesis of 2-(3-hydroxyalkyl)-1-pyrrolines is contemplated, other approaches are required such as the condensation of 2-methoxy-1-pyrrolines with acetylbutyrolactones, followed by acid hydrolysis,[4] or addition reactions to 1-pyrrolinium salts.[10] To date, no examples are known regarding the synthesis of 2-(3-hydroxyalkyl)-1-pyrrolines starting from 2-methyl-1-pyrroline.

In the present report, the utility of 2-methyl-1-pyrroline as a substrate for the synthesis of functionalized pyrrolines and pyrrolidines bearing an oxygenated side-chain at the 2-position will be discussed. For this purpose, α-lithiated 2-methyl-1-pyrroline was quenched with electrophiles in which both a chloroalkane moiety and either a carbonyl or a masked carbonyl group is present, leading to two different classes of compounds via different reaction mechanisms.

2. Results and discussion

1-Azaallylic anions comprise an extremely useful class of reactive synthons for further elaboration due to their ability to form new carbon–carbon bonds with minimal side reactions.[11] Although little information can be found regarding the reactivity of 1-azaallylic anions towards α-halogenated carbonyl compounds, the synthesis of pyrroles has been described in this way utilizing *N*-(ethylidene)amines and α-haloketones.[12] The underlying mechanism has been explained as an S_N2 reaction of the α-metalated imine with the halomethyl derivative, followed by cyclization of the enamine form and elimination of water. The reaction of the aza-enolate derived from *N*-(isopropylidene)cyclohexylamine with chloroacetone also resulted in a pyrrole derivative, although in this

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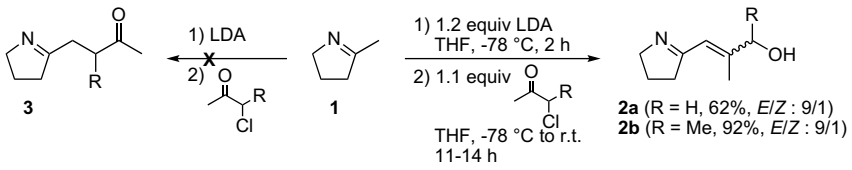
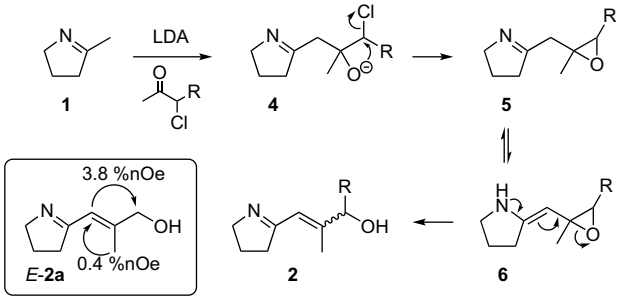


Scheme 1.

case an initial nucleophilic addition across the carbonyl was observed.[12] As this methodology has not been applied before on cyclic imines, 2-methyl-1-pyrroline **1** was evaluated as a synthon for the preparation of bicyclic systems such as pyrrolizine derivatives upon consecutive treatment with a strong base and a α-haloketone. Thus, the 1-azaallylic anion derived from 2-methyl-1-pyrroline (**1**) by the treatment with 1.2 equiv of lithium diisopropylamide (LDA) in THF was quenched with 1.1 equiv of chloroacetone or 3-chloro-2-butanone, affording—quite surprisingly—2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines **2a**,**b** as 9/1 mixtures of *E*/*Z*-isomers after 11–14 h reaction at room temperature (Scheme 1). ^{1}H NMR analysis of the reaction mixture obtained immediately after workup (for R=H) suggested the formation of an epoxide, which easily rearranged into 1-pyrroline **2a** upon standing at room temperature for 11–14 h.

The unexpected molecular structure of pyrrolines **2** was confirmed by detailed spectroscopic analysis, pointing to a peculiar reaction mechanism. According to the previously reported reactivity of acyclic lithiated imines and α-haloketones,[12] alkylation of 2-methyl-1-pyrroline with α-chloroketones was expected to afford 2-(3-oxobutyl)-1-pyrrolines **3** (Scheme 1). Instead, nucleophilic addition of the 1-azaallylic anion derived from 2-methyl-1-pyrroline across the carbonyl moiety in α-chloroketones results in adducts **4**, followed by epoxide formation through nucleophilic displacement of chloride by the in situ formed alkoxide anion (Scheme 2). Direct nucleophilic substitution of lithiated 2-methyl-1-pyrroline at the chlorinated carbon atom of chloroacetone, followed by enolization and migration of the double bond into conjugation with the imine would lead to 2-(3-hydroxy-1-butenyl)-1-pyrroline, which was never observed under the reaction conditions. This fact, in combination with the intermediacy of epoxides **5**, excludes this alternative mechanism.



Scheme 2.

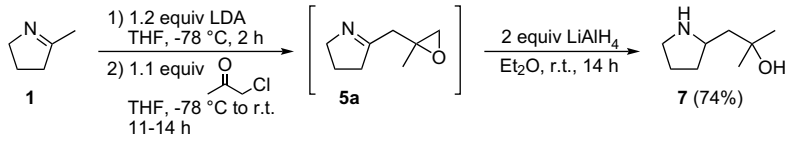
The ring opening of epoxides **5** can be explained considering their imine (**5**)—enamine (**6**) tautomerism, furnishing 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines **2** as the final products. The *E*-isomer *E*-**2a** could be obtained in pure form via recrystallization from diethyl ether, allowing the performance of NOE-experiments in order to establish its relative stereochemistry (Scheme 2). Spontaneous isomerization of *E*-**2a** to a 1/1 mixture of *E*/*Z*-isomers was observed upon standing at room temperature.

The intermediacy of the reactive epoxides **5** in this peculiar transformation was further substantiated by adding 2 equiv of lithium aluminium hydride to the reaction mixture obtained after treatment of 2-methyl-1-pyrroline (**1**) with LDA and chloroacetone, resulting in 2-(2-hydroxy-2-methylpropyl)pyrrolidine (**7**) via reduction of the imino moiety and hydride-induced ring opening at the unsubstituted epoxide carbon atom in oxirane **5a** (Scheme 3). It is worth mentioning that the 2-(2-hydroxyalkyl)pyrrolidine motif is present in several naturally occurring compounds such as the alkaloids (pseudo-)hygroline[13] and dihydrocuscohygrine.[14] Recently, 1-aryl-2-(2-hydroxyethyl)pyrrolidines have also been described as oxidative hair dyes.[15]

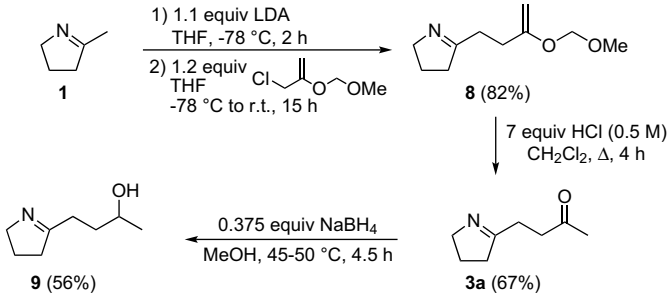
Based on the above-described findings, the straightforward synthesis of 2-(3-oxobutyl)-1-pyrroline (**3a**) (Scheme 1, R=H) through α-alkylation of 2-methyl-1-pyrroline with chloropropanone cannot be realized, meaning that other approaches should be devised. Due to the peculiar reactivity of the azaallylic anion derived from 2-methyl-1-pyrroline towards α-chloroketones, 2-methyl-1-pyrroline (**1**) was treated with 3-chloro-2-(methoxymethyloxy)-1-propene as a masked α-chloroketone under similar reaction conditions. The latter electrophile was easily prepared from 1,3-dichloro-2-(methoxymethyloxy)propane through a dehydrochlorination process.[16]

Thus, treatment of 2-methyl-1-pyrroline (**1**) with 1.1 equiv of LDA and 1.2 equiv of 3-chloro-2-(methoxymethyloxy)-1-propene in THF afforded the corresponding alkylated pyrroline **8** in 82% yield after 15 h at room temperature. Subsequent hydrolysis of the acetal moiety in the latter pyrroline **8** by means of 7 equiv of an aqueous solution of hydrochloric acid (0.5 M) yielded the desired γ-iminoketone **3a** after reflux for 4 h in a dichloromethane/water solvent system (Scheme 4). Consequently, the use of 3-chloro-2-(methoxymethoxy)-1-propene provides a convenient alternative for the hypothetical alkylation of 2-methyl-1-pyrroline by means of chloroacetone.

Finally, ketone **3a** was reduced towards the corresponding alcohol upon careful treatment with 0.375 molar equivalents of sodium borohydride (i.e., 1.5 equiv of hydride) in methanol, affording 2-(3-hydroxybutyl)-1-pyrroline **9**[4b] after 4.5 h at 45–50 °C (Scheme 4). It should be noted that the scale had to be limited to 0.5 mmol and the reaction temperature had to be controlled carefully



Scheme 3.



Scheme 4.

(45–50 °C) in order to achieve a selective reduction of γ-iminoketone **3a** into γ-hydroxyimine **9**.

In conclusion, the synthesis of 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines through condensation of 2-methyl-1-pyrroline with chloroacetone or 3-chloro-2-butanone using LDA in THF via a new and peculiar reaction mechanism has been described. The intermediacy of 2-(2,3-epoxy-2-methylalkyl)-1-pyrrolines in the latter transformation was demonstrated by immediate reductive epoxide ring opening utilizing lithium aluminium hydride in diethyl ether. As a convenient alternative for the preparation of the anticipated 2-(3-oxobutyl)-1-pyrrolines, the alkylation of 2-methyl-1-pyrroline with 3-chloro-2-(methoxymethyloxy)-1-propene using LDA in THF, followed by acid hydrolysis, has been shown to afford 2-(3-oxobutyl)-1-pyrroline, which was subsequently reduced by sodium borohydride in methanol towards the corresponding 2-(3-hydroxybutyl)-1-pyrroline.

3. Experimental part

3.1. General

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectro meter (VARIAN MAT 112, 70 eV) using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a Perkin Elmer 1310 spectrophotometer or a Spectrum One FT-IR. Elemental analyses were performed with a PerkinElmer Series II CHNS/O Analyzer 2400. Dichloromethane was dried over calcium hydride, while diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

3.2. Synthesis of 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrrolines 2

General procedure: to a solution of diisopropylamine (24 mmol) in dry THF (20 mL) at 0 °C was added slowly via a septum *n*-butyllithium (24 mmol, 2.5 M in hexane) under nitrogen atmosphere. After 5 min, the solution was cooled to −78 °C and 2-methyl-1-pyrroline **1** (20 mmol), dissolved in dry THF (20 mL), was added dropwise. The reaction mixture was then stirred for 2 h at −78 °C. Finally, a solution of α-chloroketone (22 mmol) in dry THF (20 mL) was added slowly, after which the reaction mixture was stirred for 14 h at room temperature. Workup was carried out by pouring the reaction mixture in an aqueous sodium hydroxide solution (75 mL, 0.5 M), followed by extraction with diethyl ether (2×75 mL, 1×50 mL). Drying of the organic phase with K_2CO_3, filtration of the drying agent and removal of the solvent in vacuo afforded intermediate 2-(2,3-epoxy-2-methylalkyl)-1-pyrroline **5** (after alkylation of 2-methyl-1-pyrroline with 3-chloro-2-butanone, no intermediate epoxide **5b** could be isolated). The resulting crude compound was left at room temperature for 11–14 h, affording 2-(3-hydroxy-2-methyl-1-alkenyl)-1-pyrroline **2** as a mixture of the *E*- and *Z*-isomer (*E*/*Z*:9/1).

3.2.1. *E*-2-(3-Hydroxy-2-methyl-1-propenyl)-1-pyrroline *E*-**2a**

Recrystallized from diethyl ether. White crystals. Yield after recrystallization: 40%. Mp 97 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.90 (3H, s), 1.90 (2H, quint, *J*=7.8 Hz), 2.71 (2H, t, *J*=8.1 Hz), 3.83 (2H, t, *J*=7.3 Hz), 4.03 (2H, s), 6.06 (1H, br s), 6.40 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.9 (CH_3), 22.8 (CH_2), 38.1 (CH_2), 59.6 (CH_2), 66.8 (CH_2), 118.5 (CH), 148.0 (C), 174.2 (C). IR (NaCl, cm^{-1}): $\nu_{C=N}$=1659, ν_{OH}=3400–2400. MS (70 eV): *m*/*z* (%): 139 (M^+, 91), 138 (13), 122 (10), 120 (20), 111 (12), 110 (26), 109 (11), 108 (100), 83 (11), 82 (19), 80 (38), 68 (10), 53 (13). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.19; H, 9.62; N, 9.93.

In the NMR spectra of the reaction mixture the following signals for the *Z*-isomer *Z*-**2a** could be distinguished. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.59 (2H, t, *J*=7.9 Hz), 3.96 (2H, t, *J*=6.9 Hz), 5.98 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.3 (CH_3), 24.7 (CH_2), 38.6 (CH_2), 60.7 (CH_2), 63.2 (CH_2), 120.7 (CH), 151.6 (C), 173.2 (C).

3.2.2. *E*-2-(3-Hydroxy-2-methyl-1-butenyl)-1-pyrroline *E*-**2b**

Crude yield: 92%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.30 (3H, d, *J*=6.3 Hz), 1.89 (2H, quint, *J*=7.8 Hz), 1.97 (3H, s), 2.68 (2H, t, *J*=8.2 Hz), 3.87 (2H, t, *J*=7.3 Hz), 4.26 (1H, q, *J*=6.5 Hz), 6.29 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.7 (CH_3), 21.8 (CH_3), 22.8 (CH_2), 38.4 (CH_2), 60.0 (CH_2), 72.5 (CH), 119.1 (CH), 151.3 (C), 173.9 (C). IR (NaCl, cm^{-1}): $\nu_{C=N}$=1670, ν_{OH}=3350–2480. MS (70 eV): *m*/*z* (%): 153 (M^+, 75), 152 (12), 134 (23), 125 (11), 108 (100), 68 (12), 53 (15).

3.2.3. 2-(2,3-Epoxy-2-methylpropyl)-1-pyrroline ***5a***

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35 (3H, s), 1.89 (2H, quint, *J*=7.1 Hz), 2.47–2.71 (6H, m), 3.81–3.86 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.2 (CH_3), 22.6 (CH_2), 38.2 (CH_2), 41.4 (CH_2), 53.6 (CH_2), 55.3 (C), 60.9 (CH_2), 174.2 (C). IR (NaCl, cm^{-1}): $\nu_{C=N}$=1637.

3.2.4. 2-(2-Hydroxy-2-methylpropyl)pyrrolidine **7**

The crude 2-(2,3-epoxy-2-methylpropyl)-1-pyrroline (**5a**) (7.2 mmol) was dissolved in dry diethyl ether (15 mL), followed by the addition of lithium aluminium hydride (14.4 mmol) at room temperature. The resulting suspension was stirred for 14 h at room temperature. Afterwards, water (2 mL) was added at 0 °C in order to neutralize the excess of $LiAlH_4$. The mixture was stirred for 10 min, after which the grey suspension was filtered over K_2CO_3 and Celite. The filter cake was then washed thoroughly with dry diethyl ether (3×20 mL). Removal of the solvent in vacuo afforded 2-(2-hydroxy-2-methylpropyl)pyrrolidine (**7**), which was purified by distillation (bp 106–110 °C/13 mmHg).

Colourless liquid. Crude yield: 74%. Yield after distillation: 39%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18 (3H, s), 1.26 (3H, s), 1.28–1.96 (4H, m), 2.78–2.99 (2H, m), 3.49–3.60 (1H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.8 (CH_2), 28.2 (CH_3), 31.7 (CH_3), 32.9 (CH_2), 45.8 (2×CH_2), 55.9 (CH), 70.3 (C). IR (NaCl, cm^{-1}): $\nu_{OH,NH}$=3560–3020. MS (70 eV): *m*/*z* (%): 143 (M^+, 2), 71 (13), 70 (100), 56 (11). HRMS: calcd for $C_8H_{18}NO$ $[M+H]^+$ 144.13883, found 144.13894.

3.2.5. 2-(3-Oxobutyl)-1-pyrroline ***3a***

To a solution of diisopropylamine (22 mmol) in dry THF (20 mL) at 0 °C was added slowly via a septum *n*-butyllithium (22 mmol, 2.5 M in hexane) under nitrogen atmosphere. After 5 min, the solution was cooled to −78 °C and 2-methyl-1-pyrroline **1** (20 mmol), dissolved in dry THF (20 mL), was added dropwise. The reaction mixture was then stirred for 2 h at −78 °C. Finally, a solution of 3-chloro-2-(methoxymethyloxy)-1-propene[16] (24 mmol) in dry THF (20 mL) was added slowly, after which the reaction mixture was stirred for 15 h at room

temperature. Workup was carried out by pouring the reaction mixture in an aqueous sodium hydroxide solution (75 mL, 0.5 M), followed by extraction with diethyl ether (2×75 mL, 1×50 mL). Drying of the organic phase with K_2CO_3, filtration of the drying agent and removal of the solvent in vacuo afforded 2-[3-(methoxymethyloxy)-3-butenyl]-1-pyrroline (**8**). The latter pyrroline **8** (1.4 mmol) was dissolved in dichloromethane (10 mL), followed by the addition of an aqueous solution of hydrogen chloride (10 mmol, 0.5 M). After reflux for 4 h under vigorous stirring, the reaction mixture was extracted with dichloromethane (3×20 mL). Drying (K_2CO_3), filtration of the drying agent and removal of the solvent in vacuo afforded 2-(3-oxobutyl)-1-pyrroline (**3a**), which was purified by distillation (bp 26 °C/0.04 mmHg). The neat compound appeared to be unstable upon prolonged preservation.

Colourless liquid. Yield after distillation: 67%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.86 (2H, quint, J=7.8 Hz), 2.19 (3H, s), 2.43–2.59 (4H, m), 2.85 (2H, t, J=6.9 Hz), 3.72–3.82 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.5 (CH_2), 26.9 (CH_2), 30.1 (CH_3), 38.0 (CH_2), 39.5 (CH_2), 60.7 (CH_2), 176.8 (C), 208.0 (C). IR (NaCl, cm^{-1}): $\nu_{C=N}$=1642, $\nu_{C=O}$=1715. MS (70 eV): m/z (%): 139 (M^+, 8), 124 (69), 121 (15), 120 (21), 97 (34), 96 (100), 84 (12), 82 (21), 80 (13), 69 (14), 68 (34). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.26; H, 9.68; N, 9.95.

3.2.6. 2-(3-Hydroxybutyl)-1-pyrroline **9**

To a solution of 2-(3-oxobutyl)-1-pyrroline (**3a**) (0.5 mmol) in dry methanol (1 mL) was added sodium borohydride (0.19 mmol). The resulting suspension was stirred for 4.5 h at 45–50 °C. Afterwards, the reaction mixture was poured into an aqueous solution of sodium hydroxide (10 mL, 0.5 M) and extracted with dichloromethane (3×10 mL). Drying (K_2CO_3), filtration of the drying agent and removal of the solvent in vacuo afforded 2-(3-hydroxybutyl)-1-pyrroline (**9**) (purity >95% by GC).

Light-yellow oil. Yield: 56%. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.19 (3H, d, J=5.9 Hz), 1.78 (2H, ~q, J=6.3 Hz), 1.82–1.96 (2H, m), 2.41–2.55 (4H, m), 3.73–3.87 (3H, m), 5.30 (1H, s). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.5 (CH_2), 23.7 (CH_3), 30.8 (CH_2), 34.9 (CH_2), 38.0 (CH_2), 60.3 (CH_2), 67.4 (CH), 179.6 (C). IR (NaCl, cm^{-1}): $\nu_{C=N}$=1644, ν_{OH}=3275. MS (70 eV): m/z (%): no M^+; 140 (M^+-1, 3), 126 (25), 124 (10), 108 (12), 98 (11), 97 (33), 96 (65), 83 (100), 82 (33), 71 (10), 55 (17).

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References and notes

1. For recent reviews, see: (a) Huang, P. Q. *Synlett* **2006**, 1133; (b) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213; (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484; (d) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142; (e) Cheng, X. C.; Wang, Q.; Fang, H.; Xu, W. F. *Curr. Med. Chem.* **2008**, *15*, 374.
2. For a few recent examples, see: (a) Torres-Sanchez, M. I.; Borrachero, P.; Cabrera-Escribano, F.; Gomez-Guillen, M.; Angulo-Alvarez, M.; Alvarez, E.; Favre, S.; Vogel, P. *Tetrahedron: Asymmetry* **2007**, *18*, 1809; (b) Peng, J.; Clive, D. L. J. *Org. Lett.* **2007**, *9*, 2939; (c) Behr, J.-B.; Gainvors-Claisse, A.; Belarbi, A. *Nat. Prod. Res., Part A* **2007**, *21*, 76; (d) Behr, J.-B.; Gainvors-Claisse, A.; Belarbi, A. *Nat. Prod. Res., Part B* **2006**, *20*, 1308.
3. Dürckheimer, W.; Martin, W.; Schrinner, E. Ger. Offen., 1974, DE 2319019; *Chem. Abstr.* **1975**, *82*, 43170.
4. (a) Provot, O.; Celerier, J.-P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992**, *57*, 2163; (b) Provot, O.; Celerier, J.-P.; Lhommet, G. *J. Heterocycl. Chem.* **1998**, *35*, 371.
5. Choi, J. R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469.
6. Cha, J. K.; Bennett, R. B., III. U.S. Patent 5,187,279 A; *Chem. Abstr.* **1993**, *118*, 255177.
7. Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921.
8. (a) Dannhardt, G.; Obergrusberger, R. *Arch. Pharm.* **1979**, *312*, 498; (b) Dannhardt, G.; Obergrusberger, R. *Arch. Pharm.* **1979**, *312*, 896; (c) Böhme, R.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1989**, 109; (d) Schuster, E.; Hesse, C.; Schumann, D. *Synlett* **1991**, 916.
9. (a) Dannhardt, G.; Lehr, M.; Steindl, L. *Chem. Ztg.* **1986**, *110*, 267; (b) Dannhardt, G.; Meindl, W.; Gussmann, S.; Ajili, S.; Kappe, T. *Eur. J. Med. Chem.* **1987**, *22*, 505; (c) Tirel, P. J.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 1947; (d) Hua, D. H.; Bharathi, S. N.; Robinson, P. D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128; (e) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Rubio, E. *J. Chem. Soc., Chem. Commun.* **1992**, 1419; (f) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, *51*, 8613; (g) Dannhardt, G.; Bauer, A.; Nowe, U. *J. Prakt. Chem.* **1998**, *340*, 256; (h) Fustero, S.; de la Torre, M. G.; Jofre, V.; Carlon, R. P.; Navarro, A.; Fuentes, A. S.; Carrio, J. S. *J. Org. Chem.* **1998**, *63*, 8825; (i) Fustero, S.; de la Torre, M. G.; Pina, B.; Fuentes, A. S. *J. Org. Chem.* **1999**, *64*, 5551; (j) Abbaspour Tehrani, K.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099; (k) Park, K.-H.; Marshall, W. J. *J. Org. Chem.* **2005**, *70*, 2075; (l) Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Roman, R.; Brodsky, B. H.; Sanchez-Rosello, M.; Acena, J. L.; Ramirez de Arellano, C. *Tetrahedron* **2006**, *62*, 1444; (m) Movassaghi, M.; Chen, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 565.
10. (a) Stavinoha, J.; Bay, E.; Leone, A.; Mariano, P. S. *Tetrahedron Lett.* **1980**, *21*, 3455; (b) Mariano, P. S.; Stavinoha, J.; Bay, E. *Tetrahedron* **1981**, *37*, 3385.
11. Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353.
12. Wittig, G.; Röderer, R.; Fischer, S. *Tetrahedron Lett.* **1973**, *14*, 3517.
13. (a) Muñoz, O.; Piovano, M.; Garbarino, J.; Hellwing, V.; Breitmaier, E. *Phytochemistry* **1996**, *43*, 709; (b) Kim, J. H.; t'Hart, H.; Stevens, J. F. *Phytochemistry* **1996**, *41*, 1319; (c) Schneider, M. J.; Brendze, S.; Montali, J. A. *Phytochemistry* **1995**, *39*, 1387; (d) Gambaro, V.; Labbr, C.; Castillo, M. *Phytochemistry* **1983**, *22*, 1838; (e) San Martin, A.; Rovirosa, J.; Gambaro, V.; Castillo, M. *Phytochemistry* **1980**, *19*, 2007.
14. Christen, P.; Roberts, M. F.; Phillipson, J. D.; Evans, W. C. *Phytochemistry* **1995**, *38*, 1053.
15. Chassot, L.; Braun, H.-J. Eur. Pat. Appl., 2007, EP 1752192 A1; *Chem. Abstr.* **2007**, *146*, 235426.
16. Gu, X. P.; Nishida, N.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192.