Synthesis of Ethyl 5-Phenyl-6-Oxa-1-Azabicyclo[3.1.0]hexane-2-carboxylate Derivatives and Evaluation of Their Antimalarial Activities

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Derivatives of ethyl 5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate (**14**−**20**), with side chains varying from three to five carbon atoms and bearing various substituents, have been prepared from ethyl 2-phenyl-1-pyrroline-5-carboxylate (**12**). Their in vitro activity against *P. falciparum* (K1 strain) and antimycobacterium and also their cytotoxic activity against Vero cell have been evaluated.

Introduction

Up to two billion people in Africa, Asia, and South America are at risk of malaria infection, and the incidence of this disease has dramatically increased since the emergence of the chloroquine-resistant strain of *Plasmodium falciparum*, the most deadly strain of malarial parasites.[1,2] In 1972, artemisinin (**1**), a highly potent antimalarial, was isolated from the leaves of *Artemisia annua* L.[3,4] Artemisinin is a sesquiterpene lactone bearing an endoperoxide moiety that is essential for its antimalarial activity. Research toward the understanding of the mechanism of action of artemisinin has been intense,[5,6] and the model proposed by Posner and co-workers has widely been used as a working hypothesis.[6c,7] It is believed that the endoperoxide moiety of artemisinin is homolytically cleaved by the Fe(II) ion in heme to produce the alkoxy radical (**2**), which undergoes a [1,5]-hydrogen shift to give the corresponding carbon-centered radical (**3**), which is believed to be responsible for the killing of parasites and hence the antimalarial activity of artemisinin (Scheme 1).[8,9] Indeed, several studies have demonstrated experimentally that cleavage of the endoperoxide bond in artemisinin by the Fe(II) ion readily takes place giving rise to many products derived from the radical intermediate **3**.[6d,10]

Recently, Black and co-workers reported that derivatives of ethyl 5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate (**4a**−**c**) reacted with Fe(II) sulfate to give the corresponding bicyclic lactams (**7a**−**c**) as shown in Scheme 2.[11] The reaction mechanism was believed to involve an iron(II)-induced homolytic cleavage of the N−O bond in **4** to form the corresponding aminyl radical (**5**), followed by cyclization via a 5-exo-trig process leading to a carbon-centered radical (**6**) and finally to the observed products.

There is an ongoing research program being conducted in our laboratories to find new leads for antimalarial and antituberculous potency from natural products and synthesis.[12,13] We noted the similarity of reactions shown in Schemes 1 and 2 involving the Fe(II)-catalyzed cleavage of O−O and N−O bonds in **1** and **4**, respectively, and their subsequent reactions providing carbon radical intermediates (e.g., **3** and **6**). Possibly the heme ferrous ion might trigger a homolytic cleavage of the N−O bond and subsequent radical shift to provide the carbon radical in **4**, mimicking that of the process observed with ferrous sulfate. It was therefore of interest to prepare derivatives of **4** bearing various side chains, including those with suitable functionality for a [1,5]-hydrogen radical shift from the carbon side chain to the emerging nitrogen radical and to test these compounds for their in vitro activity against chloroquine-resistant *Plasmodium falciparum* K1 strain.

Results and Discussion

The synthesis of compounds **14**−**20**,[11,14] outlined in Schemes 3 and 4, involved three key reaction steps: first the formation of 1-pyrroline derivative **12**, followed by base-catalyzed alkylation at position 5, and last, construction of the oxaziridine moiety. Hence, the well-established reductive cyclization of the γ-nitrocarbonyl compound **10** with cold aqueous ammonium chloride and zinc dust provided, via intermediate **11**, the prerequisite 1-pyrroline **12**,[15] which upon treatment with sodium hydride in a mixture of DMF/THF in a ratio of 1:10 at room temperature followed by an alkyl halide furnished the corresponding alkylated products **13a**−**f** (Scheme 3).

Treatment of **12** with methyl 4-bromocrotonate under the conditions of the above-mentioned sodium hydride catalyzed alkylation reaction gave a mixture of several products. However, treatment of **12** with lithium diisopropylamide (LDA) at −78 °C in THF followed by methyl 4-bromocrotonate provided not the product of a direct S_N2 displacement but the cyclopropane derivative **13g** as the only product isolated (64%). Compound **13g** apparently resulted from the Michael initiated ring closure (MIRC) reaction, which involved a consecutive Michael addition of the anion derived from **12** to methyl 4-bromocrotonate, followed by displacement of the bromide ion by the emerging ester enolate.[16] The trans-stereochemical relationship of the cyclopropane ring in

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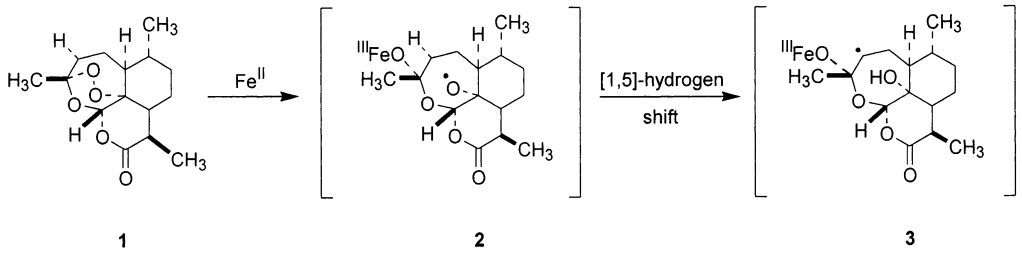
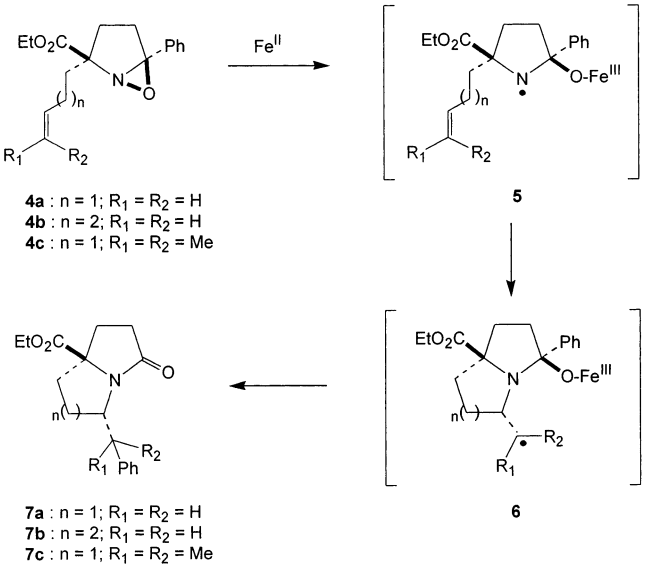
Scheme 1



1 2 3

Scheme 2



13g was deduced from the coupling constant (J = 4.5 Hz) between the two adjacent protons on the cyclopropane moiety.

Synthesis of 6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylates (**14**−**20**) was finally completed by oxidation of the alkylated pyrrolines (**13a**−**g**), employing magnesium monoperoxyphthalate in methanol as shown. In all cases, two isomeric oxaziridines were obtained, with the cis isomers (**14a**−**20a**) predominating. Apparently, oxidation by the peracid took place more readily on the less hindered face of the pyrroline molecule opposite that of the sterically more demanding ester functionality. The stereochemical integrity of the products was established by nuclear Overhauser effect (NOE) experiments in which each of the major isomers (**14a**−**20a**) showed signal enhancement between ortho protons on the phenyl ring and the methyl group of ethyl ester. No such interaction was observed in any of the minor isomers (**14b**−**20b**). The stereochemical integrity of compound **20a** was also further confirmed by X-ray crystallography.[17]

To investigate the behavior toward the ferrous ion of the 6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate derivatives synthesized by the route shown above, both isomers of compounds **14**, **16**, **18**, and **20** were selected as examples for our study. Treatment of compounds **14a**, **16a**, **18a**, and **20a** with ferrous ion under the conditions described in the literature[14,18] (ferrous(II) sulfate in refluxing ethanol) produced the corresponding pyrrolines **13a**,**c**,**e**,**g** in good yields. Likewise the trans isomers, **14b**, **16b**, **18b**, and **20b** provided the same products but only in moderate yields (Scheme 5).

Table 1. Antimalarial, Antituberculous, and Cytotoxic Activities of Compounds **4a**−**c**, **14a**−**20a**, and **14b**−**20b**[a]

compd	antimalarial activity[b] EC_{50} (μg/mL)	antituberculous activity[c] MIC (μg/mL)	cytotoxicity[d] IC_{50} (μg/mL)
4a	44.2	*e*	*e*
4b	13.9	*e*	*e*
4c	21.9	*e*	*e*
14a	inactive	200	>50
14b	4.6	200	>50
15a	inactive	100	>50
15b	21.7	100	28.9
16a	inactive	100	inactive[g]
16b	2.4	100	inactive[g]
17a	inactive	100	>50
17b	3.1	100	inactive[g]
18a	inactive	25	>50
18b	2.9	200	inactive[g]
19a	inactive	inactive[f]	>50
19b	14.7	200	>50
20a	inactive	200	>50
20b	15.9	100	43.4

[a] All biological activities resulted from the average of multiple (three) determinations. [b] EC_{50} values of the standard antimalarial compounds chroloquine diphosphate and artemisinin were 0.16 and 0.0011 μg/mL, respectively. [c] The MIC value of the standard drug isoniazide was 0.050 μg/mL. [d] The IC_{50} value of the standard compound elipticine was 1.0 μg/mL for the Vero cell. [e] Antituberculous activity and cytotoxicity were not tested. [f] Inactive at up to 200 μg/mL. [g] Inactive at less than 50 μg/mL.

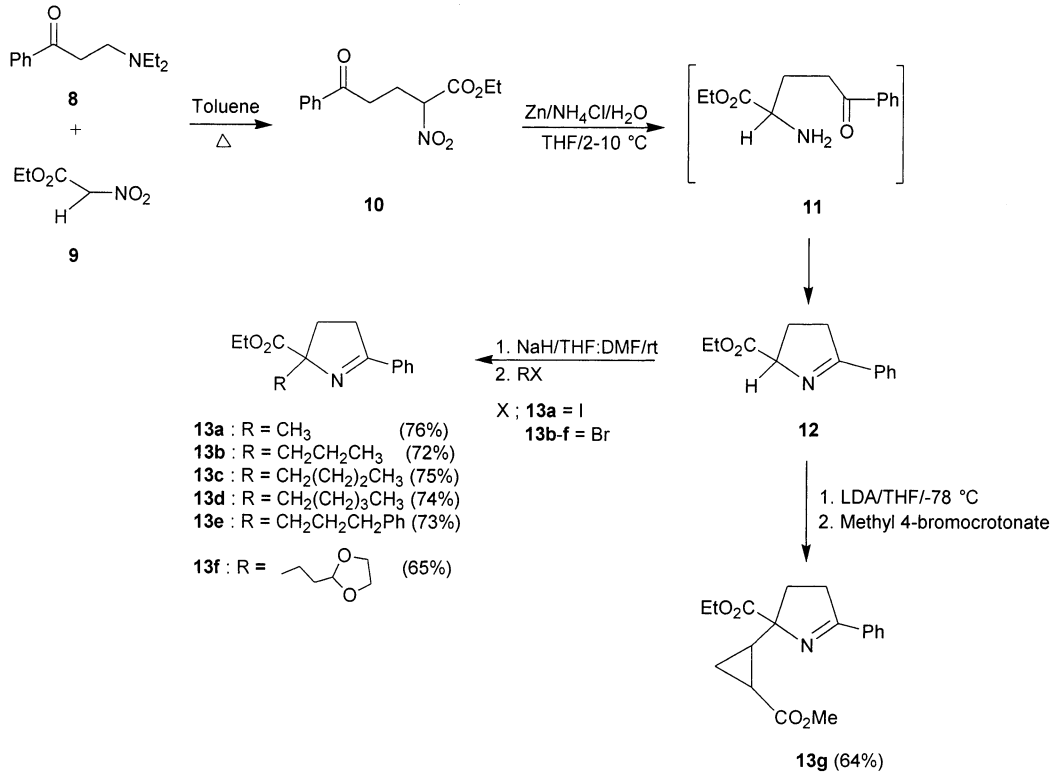
Formation of the pyrroline **13** could be explained in terms of ferrous ion induced homolytic fission of the oxaziridine N−O bond of the starting material to give initially the aminyl radical **21** and subsequently the oxoiron species **22**. Collapse of the O−Fe^{III} bond would give rise to the aminol **23**, which would undergo dehydration to the observed pyrroline **13** as outlined in Scheme 6.

Biological Activities

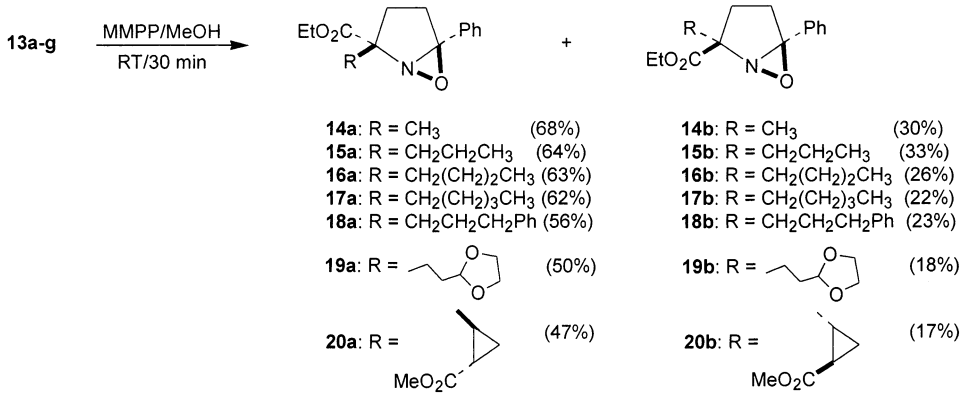
All compounds prepared as described above were subjected to an in vitro malaria screening system against *P. falciparum* (K1 multidrug resistant strain), and the assay was performed following the microculture radioisotope technique as described by Desjardins[19] using both chloroquine diphosphate and artemisinin as standards. Growth inhibitory activity against *M. tuberculosis* H37R was performed using the microplate Alamar Blue assay (MABA).[20] Cytotoxicity of the purified compounds against African green monkey kidney fibroblast (Vero cell) was evaluated by using the colorimetric method.[21]

Cytotoxic, antimalarial, and antituberculous activities of 6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate derivatives **4a**−**c**, **14a**−**20a**, and **14b**−**20b** are shown in Table 1. It can be seen that almost all of the tested compounds

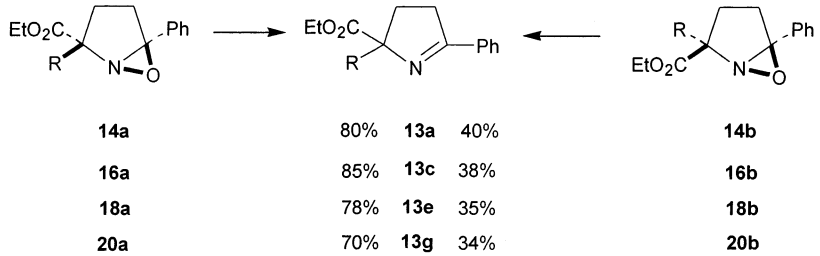
Scheme 3



Scheme 4



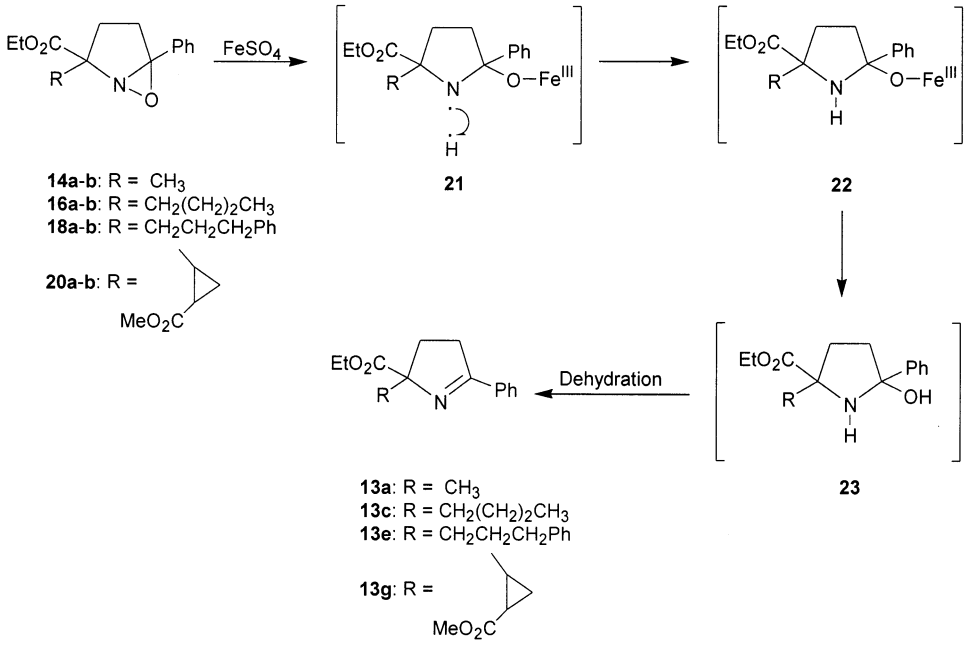
Scheme 5



exhibited very low cytotoxic activity against Vero cell with IC_{50} values of >50 μg/mL while compounds **15b** and **20b** were weakly active with the IC_{50} values of 28.9 and 43.4 μg/mL, respectively. These substances, with the exception of **18a**, exhibited weak antimycobacterium activity having MIC values in the range 100−200 μg/mL. Three trans isomers, **4a**, **4b**, and **4c**, synthesized earlier[14] were also subjected to in vitro antimalarial testing, and their EC_{50} values were 44.2, 13.9, and 21.9 μg/mL, respectively.

Most interesting are the resulting of compounds **14**−**20** whereupon all trans isomers (**14b**−**20b**) showed respectable antimalarial activity while the cis isomers (**14a**−**20a**) were inactive. The observed marked contrast clearly indicated that the antimalarial activity of 6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate derivatives de-

Scheme 6



pends on their stereochemistry. It is quite possible that the trans isomers, having a syn relationship between the ester group and the oxaziridine moiety, bind to the heme ferrous ion much better than their counterparts (Figure 1).

Our conclusion regarding the structure−activity relationship of cis and trans isomers of 6-oxa-1-azabicyclo-[3.1.0]hexane-2-carboxylates **14a**−**20a** and **14b**−**20b**, respectively, is not without precedence. It is generally accepted that scission of the artemisinin's peroxide bond by Fe(II) in heme leads to an intermediate oxyradical followed by a [1,5]-hydrogen shift to provide the carbon radical (Scheme 1), which is important for the killing of parasites. Avery and co-workers,[22] using theoretical molecular modeling calculations, reported the structure−activity relationship of several artemisinin derivatives whereupon the better binding between the peroxide moiety and Fe(II) in heme resulted in superior activity of the studied compounds.

An additional speculation is that there could be a selectively and stereochemically controlled formation of carbon radicals following the ring opening of the oxaziridines. In this respect, the rearrangement shown in Scheme 2 occurs only for oxaziridines in which the alkenyl group is trans to the oxaziridine ring.[11] The corresponding cis isomers simply undergo deoxygenation to the related pyrrolines.[14] Therefore, the implication is that the radical-transfer process resulting in the formation of the carbon radical only occurs when the new carbon−nitrogen bond can take place from the side opposite the breaking oxaziridine ring. In the case of the oxaziridines **14**−**20**, it could be that hydrogen abstraction could generate a carbon radical (possibly enhancing for antimalarial activity) provided that the new hydrogen−nitrogen bond can form on the side opposite to the breaking oxaziridine ring. Thus, only the trans isomers **14b**−**20b** could do this and consequently show antimalarial activity. However, although much lower yields of pyrrolines **13** were obtained from trans isomers **14b**−**20b** than from the cis isomers **14a**−**20a**, no specific products implying carbon radical formation were detected.

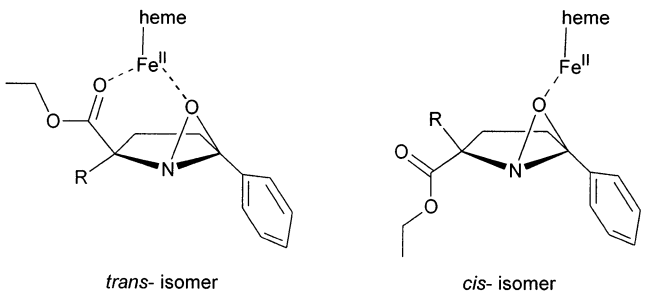


Figure 1.

In conclusion, derivatives of ethyl 2-alkyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate have been synthesized by base-catalyzed alkylation of 1-pyrroline, followed by oxidation of the corresponding pyrroline to give cis and trans isomers. These compounds showed weak antituberculous and cytotoxic activities. However, while the trans isomers (**14b**−**20b**) exhibited in vitro antimalarial activities against *P. falciparum*, the cis counterparts were inactive. Results from this study indicate that the trans isomers of oxaziridine derivatives can be used as a structural lead for an exploration to find new antimalarial structural entities.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 300 and 400 MHz spectrometers in $CDCl_3$ using TMS as the internal standard. Infrared spectra were recorded on an FT-IR system 2000 (Perkin-Elmer) spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer and a Perkin-Elmer series PE2400 elemental analyzer. Mass spectra were recorded on Bruker Esquire and Finnigan MAT INCOS 50 mass spectrometers. Merck silica gel 60 P_{254} was used for TLC. Solvents were distilled before used. Dried, oxygen-free THF (freshly distilled from sodium/benzophenone) was used in all experiments. Lithium diisopropylamide (LDA) was prepared by the conventional method using *n*-butyllithium

(purchased from Metallgesellschaft AG; molarity was determined by titration with 2,5-dimethoxybenzyl alcohol) and diisopropylamine in THF solution. Reactions were carried out under nitrogen atmosphere.

Ethyl 2-Nitro-5-phenyl-5-oxopentanoate 10. Compound **10** was prepared from α-diethylaminopropiophenone (**8**) and ethyl nitroacetate (**9**) according to the published procedure:[14] 98% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.45 (m, 1H), 7.35 (m, 2H), 5.28 (t, J = 7.3 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.05 (m, 2H), 2.55 (m, 2H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 164.3, 136.1, 133.4, 128.6, 127.8, 86.8, 62.9, 33.5, 24.4, 13.7; IR ($CHCl_3$) 2985, 1748, 1688, 1563, 1449, 1370, 1023, 859, 750, 690 cm^{-1}; MS (EIMS) *m/e* 265 (M^+, 0.09%), 235 (3), 218 (5), 173 (2), 146 (3), 117 (2), 105 (100), 77 (53), 51 (12).

Ethyl 2-Phenyl-1-pyrroline-5-carboxylate 12. Compound **12** was prepared from **10** according to the published procedure.[14]

General Procedure for the C5 Alkylation of Ethyl 5-Alkyl-2-phenyl-1-pyrroline-5-carboxylates 13a−f. C5-Alkyl 2-phenyl-1-pyrroline-5-carboxylate derivatives were synthesized according to the published procedure.[14]

Ethyl 5-methyl-2-phenyl-1-pyrroline-5-carboxylate 13a: 76% yield; yellow oil;[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.40 (m, 3H), 4.20 (m, 2H), 3.10 (m, 2H), 2.30 (m, 1H), 2.06 (m, 1H), 1.72 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 130.5, 129.2, 128.4, 127.6, 81.2, 62.2, 29.9, 28.2, 21.3, 14.0.

Ethyl 5-propyl-2-phenyl-1-pyrroline-5-carboxylate 13b: 72% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.45 (m, 3H), 4.25 (q, J = 7.1 Hz, 2H), 3.05 (m, 2H), 2.45 (m, 1H), 1.95 (m, 3H), 1.45 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 173.5, 130.8, 128.5, 128.4, 128.1, 83.5, 61.0, 41.0, 35.5, 31.2, 17.5, 14.4, 14.1; IR ($CHCl_3$) 2964, 2875, 1724, 1616, 1577, 1448, 1369, 1342, 1298, 1178, 1159, 1049, 1025, 693 cm^{-1}; ESI TOF MS exact mass calcd for $C_{16}H_{21}NO_2$ *m/e* 282.1470 $(M + Na)^+$, found 282.1467.

Ethyl 5-butyl-2-phenyl-1-pyrroline-5-carboxylate 13c: 75% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.44 (m, 3H), 4.23 (q, J = 7.0 Hz, 2H), 3.15 (m, 2H), 2.50 (m, 1H), 2.02 (m, 3H), 1.35 (m, 4H), 1.30 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 173.5, 134.2, 130.6, 128.2, 127.9, 83.6, 60.8, 38.5, 35.5, 31.2, 26.4, 22.9, 14.1, 13.9; IR ($CHCl_3$) 3060, 2956, 2871, 1728, 1615, 1576, 1449, 1367, 1342, 1269, 1244, 1206, 1176, 1156, 760, 693 cm^{-1}; MS (ESI TOF) *m/e* 296.27 $(M + Na)^+$. Anal. ($C_{17}H_{23}NO_2$) C, H, N.

Ethyl 5-pentyl-2-phenyl-1-pyrroline-5-carboxylate 13d: 74% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.36 (m, 3H), 4.15 (q, J = 7.1 Hz, 2H), 2.97 (m, 2H), 2.41 (m, 1H), 1.86 (m, 3H), 1.25 (m, 6H), 1.20 (t, J = 7.1 Hz, 3H), 0.80 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 173.5, 134.2, 130.6, 128.2, 127.9, 83.6, 60.9, 38.8, 35.4, 32.0, 31.2, 23.9, 22.4, 14.1, 13.9; IR ($CHCl_3$) 3029, 2959, 2932, 2862, 1724, 1615, 1576, 1449, 1342, 1236, 1196, 1179, 860, 693 cm^{-1}; ESI TOF MS exact mass calcd for $C_{18}H_{25}NO_2$ *m/e* 310.1783 $(M + Na)^+$, found 310.1792.

Ethyl 5-(3-phenylpropyl)-2-phenyl-1-pyrroline-5-carboxylate 13e: 73% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.35 (m, 3H), 7.18 (m, 2H), 7.09 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 2.97 (m, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.41 (m, 1H), 1.92 (m, 3H), 1.63 (m, 2H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.9, 142.1, 130.8, 128.7, 128.5, 128.4, 128.2, 128.0, 125.7, 83.5, 61.0, 38.4, 36.0, 35.6, 31.2, 26.1, 14.2; IR ($CHCl_3$) 3439, 3029, 3013, 2940, 1732, 1497, 1463, 1453, 1372, 1356, 1265, 1191, 1098, 786, 760, 697, 664 cm^{-1}; MS (EIMS) *m/e* 335 (M, 24.9%), 334 (100), 278 (61), 217 (7), 105 (42), 91 (77), 77 (55), 51 (14); ESI TOF MS exact mass calcd for $C_{22}H_{25}NO_2$ *m/e* 358.1783 $(M + Na)^+$, found 358.1760.

Ethyl 5-[2-(1,3-dioxolan-2-yl)ethyl]-2-phenyl-1-pyrroline-5-carboxylate 13f: 65% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.35 (m, 3H), 4.82 (t, J = 4.5 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.40 (m, 4H), 3.10 (m, 2H), 2.48 (m, 1H), 2.05 (m, 3H), 1.70 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 174.5, 173.2, 131.1, 128.4, 128.2, 128.1, 104.3, 82.8, 64.9, 64.8, 61.1, 35.5, 32.6, 31.3, 28.8, 14.1; IR ($CHCl_3$) 3014, 2964, 2889, 1727, 1614, 1577, 1449, 1370, 1343, 1144, 1025, 944, 786, 693, 671 cm^{-1}; MS (ESI TOF) *m/e* 318.17 $(M + H)^+$. Anal. ($C_{18}H_{23}NO_4$) C, H, N.

Ethyl 5-(2-methoxycarbonylcyclopropyl)-2-phenyl-1-pyrroline-5-carboxylate 13g: synthesized by published procedure;[16] 64% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H), 7.42 (m, 3H), 4.22 (m, 2H), 3.70 (s, 3H), 3.08 (m, 2H), 2.55 (m, 1H), 2.20 (m, 1H), 2.09 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.10 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 174.7, 173.5, 133.7, 131.0, 128.4, 128.1, 80.9, 61.2, 51.7, 35.7, 33.2, 29.3, 17.1, 14.1, 10.4; IR ($CHCl_3$) 3030, 2954, 2360, 2342, 1725, 1614, 1578, 1449, 1397, 1368, 1344, 1325, 1271, 1206, 1176, 1065, 1019, 786, 692 cm^{-1}; MS (ESI TOF) *m/e* 316.15 $(M + H)^+$. Anal. ($C_{18}H_{21}NO_4$) C, H, N.

General Procedure for the Preparation of Oxaziridine 14−20 via the Action of MMPP on 1-Pyrrolines 13a−g. The 6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate derivatives were synthesized by the published procedure.[14,15]

***cis*-Ethyl 2-methyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 14a:** 68% yield; yellow oil;[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.40 (m, 3H), 4.20 (m, 2H), 2.68 (m, 2H), 2.08 (m, 1H), 1.72 (m, 1H), 1.63 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 134.9, 129.3, 128.3, 126.8, 89.1, 73.4, 61.4, 31.6, 29.7, 20.6, 14.0; IR ($CHCl_3$) 3068, 2996, 2942, 1734, 1495, 1451, 1376, 1354, 1277, 1235, 1129, 1016, 887, 858 cm^{-1}; ESI TOF MS exact mass calcd for $C_{14}H_{17}NO_3$ *m/e* 270.1106 $(M + Na)^+$, found 270.1102.

***trans*-Ethyl 2-methyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 14b:** 34% yield; yellow oil;[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.40 (m, 3H), 4.35 (m, 2H), 2.75 (m, 1H), 2.52 (m, 1H), 2.25 (m, 1H), 1.83 (m, 1H), 1.43 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 134.6, 129.6, 128.4, 127.1, 87.4, 72.9, 61.4, 28.7, 27.4, 21.0, 14.2; IR ($CHCl_3$) 3068, 2997, 2940, 1732, 1498, 1451, 1375, 1354, 1276, 1235, 1129, 1016, 888, 858 cm^{-1}; ESI TOF MS exact mass calcd for $C_{14}H_{17}NO_3$ *m/e* 270.1106 $(M + Na)^+$, found 270.1101.

***cis*-Ethyl 2-propyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 15a:** 64% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.35 (m, 3H), 4.20 (m, 2H), 2.63 (m, 1H), 2.55 (m, 1H), 2.05 (m, 1H), 1.93 (m, 2H), 1.60 (m, 2H), 1.34 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 134.9, 129.3, 128.3, 126.9, 88.5, 77.2, 61.3, 37.6, 30.5, 29.2, 18.5, 14.5, 14.1; IR ($CHCl_3$) 2965, 2935, 2875, 1728, 1466, 1453, 1370, 1357, 1299, 1274, 1182, 1124, 1018, 886, 882 cm^{-1}; ESI TOF MS exact mass calcd for $C_{16}H_{21}NO_3$ *m/e* 298.1419 $(M + Na)^+$, found 298.1415.

***trans*-Ethyl 2-propyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 15b:** 33% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.35 (m, 3H), 4.30 (m, 2H), 2.83 (dd, J = 14.5, 8.4 Hz, 1H), 2.50 (ddd, J = 14.5, 10.4, 8.6 Hz, 1H), 2.20 (ddd, J = 13.0, 10.4, 8.4 Hz, 1H), 1.82 (dd, J = 13.0, 8.6 Hz, 1H), 1.78 (m, 1H), 1.63 (m, 2H), 1.43 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 133.4, 129.3, 128.3, 126.9, 86.2, 77.3, 61.3, 37.6, 30.5, 29.2, 18.5, 14.5, 14.1; IR ($CHCl_3$) 3020, 2964, 2938, 2861, 1732, 1603, 1497, 1453, 1373, 1356, 1265, 1190, 1098, 1020, 888, 859, 723, 697 cm^{-1}; MS (ESI TOF) *m/e* 298.24 $(M + Na)^+$. Anal. ($C_{16}H_{21}NO_3$) C, H, N.

***cis*-Ethyl 2-butyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 16a:** 63% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.40 (m, 3H), 4.25 (m, 2H), 2.70 (m, 1H), 2.58 (m, 1H), 2.08 (m, 1H), 1.95 (m, 2H), 1.70 (m, 2H) 1.40 (m, 3H), 1.26 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 135.4, 129.7, 128.8, 127.4, 88.9, 77.7, 61.7, 35.6, 30.9, 29.6, 27.8, 23.5, 14.5, 14.3; IR ($CHCl_3$) 3031, 2961, 2931, 1736, 1612, 1576, 1499, 1370, 1345, 1206, 1180, 1140, 1096, 1076, 1020, 727, 671 cm^{-1};

MS (ESI TOF) *m/e* 312.23 $(M + Na)^+$. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

***trans*-Ethyl 2-butyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 16b:** 26% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.40 (m, 3H), 4.30 (m, 2H), 2.64 (dd, J = 14.5, 8.6 Hz, 1H), 2.40 (ddd, J = 14.5, 10.6, 8.6 Hz, 1H), 2.25 (ddd, J = 13.6, 10.6, 8.6 Hz, 1H), 1.79 (dd, J = 13.6, 8.6 Hz, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.30 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.2, 129.9, 128.8, 127.6, 88.3, 77.7, 61.7, 35.1, 28.2, 27.6, 26.9, 23.3, 14.7, 14.2; IR ($CHCl_3$) 3031, 2961, 2931, 1736, 1612, 1576, 1449, 1370, 1345, 1206, 1180, 1140, 1096, 1076, 1020, 727, 671 cm^{-1}; MS (ESI TOF) *m/e* 312.23 $(M + Na)^+$. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

***cis*-Ethyl 2-pentyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 17a:** 62% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.39 (m, 3H), 4.21 (m, 2H), 2.66 (m, 1H), 2.51 (m, 1H), 2.08 (m, 1H), 1.93 (m, 2H), 1.71 (m, 2H), 1.38 (m, 5H), 1.26 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 134.9, 129.2, 128.3, 126.9, 88.4, 77.2, 61.2, 35.4, 32.1, 30.4, 29.2, 24.8, 22.4, 14.1, 13.9; IR ($CHCl_3$) 3031, 2959, 2931, 2873, 1728, 1615, 1499, 1453, 1357, 1328, 1279, 1260, 1236, 1199, 1017, 786, 696 cm^{-1}; ESI TOF MS exact mass calcd for $C_{18}H_{25}NO_3$ *m/e* 326.1726 $(M + Na)^+$, found 326.1734.

***trans*-Ethyl 2-pentyl-5-phenyl-6-oxa-1-azabicyclo[3.1.0]-hexane-2-carboxylate 17b:** 22% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.39 (m, 3H), 4.32 (m, 2H), 2.77 (m, 1H), 2.49 (m, 1H), 2.21 (m, 1H), 1.86 (m, 2H), 1.63 (m, 1H), 1.42 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.28 (m, 4H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 134.7, 129.5, 128.7, 127.1, 87.8, 77.0, 61.3, 34.9, 31.9, 29.7, 24.0, 22.4, 22.2, 14.3, 13.8; IR ($CHCl_3$) 3031, 2959, 2931, 2873, 1728, 1449, 1453, 1357, 1260, 1217, 1199, 1179, 1076, 1017, 887, 859, 786, 696 cm^{-1}; MS (ESI TOF) *m/e* 304.19 $(M + H)^+$. Anal. ($C_{18}H_{25}NO_3$) C, H, N.

***cis*-Ethyl 2-(3-phenylpropyl)-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 18a:** 56% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.45 (m, 3H), 7.35 (m, 2H), 7.25 (m, 3H), 4.25 (m, 2H), 2.74 (m, 3H), 2.58 (m, 1H), 2.09 (m, 4H), 1.79 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 141.9, 134.8, 129.2, 128.3, 128.2, 128.1, 126.8, 125.6, 88.5, 76.9, 61.2, 35.9, 34.8, 30.4, 29.1, 26.7, 14.0; IR ($CHCl_3$) 3066, 3029, 3013, 2940, 1730, 1603, 1497, 1453, 1372, 1357, 1332, 1265, 1188, 1097, 1017, 786, 729, 697, 664 cm^{-1}; MS (ESI TOF) *m/e* 374.17 $(M + Na)^+$. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

***trans*-Ethyl 2-(3-phenylpropyl)-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 18b:** 23% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.43 (m, 3H), 7.38 (m, 2H), 7.28 (m, 1H), 7.14 (m, 2H), 4.34 (m, 2H), 2.71 (m, 1H), 2.63 (t, J = 7.0 Hz, 2H), 2.43 (m, 1H), 2.21 (m, 1H), 1.88 (m, 3H), 1.71 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 141.2, 134.6, 129.5, 128.9, 128.3, 128.2, 127.7, 127.1, 87.8, 77.0, 61.3, 35.6, 34.3, 27.7, 27.4, 25.7, 14.4; IR ($CHCl_3$) 3029, 3012, 2987, 2940, 1732, 1603, 1497, 1453, 1393, 1356, 1333, 1179, 1098, 1019, 759, 698, 659 cm^{-1}; MS (ESI TOF) *m/e* 374.17 $(M + Na)^+$. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

***cis*-Ethyl 2-[2-(1,3-dioxolan-2-yl)ethyl]-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 19a:** 50% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.35 (m, 3H), 4.90 (m, 1H), 4.25 (m, 2H), 3.85 (m, 4H), 2.55 (m, 1H), 2.40 (m, 1H), 2.02 (m, 2H), 1.50 (m, 4H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 134.8, 129.3, 128.3, 126.9, 104.2, 88.6, 77.4, 64.9, 61.4, 30.4, 29.6, 29.3, 29.2, 14.1; IR ($CHCl_3$) 3534, 3067, 3014, 2985, 2888, 2762, 1731, 1499, 1475, 1452, 1393, 1359, 1264, 1142, 1022, 1017, 765, 760, 696, 664 cm^{-1}; ESI TOF MS exact mass calcd for $C_{18}H_{23}NO_5$ *m/e* 334.1634 $(M + H)^+$, found 334.1676.

***trans*-Ethyl 2-[2-(1,3-dioxolan-2-yl)ethyl]-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 19b:** 18% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.25 (m, 3H), 4.78 (t, J = 4.0 Hz, 1H), 4.20 (m, 2H), 3.80 (m, 4H), 2.56 (m, 1H), 2.40 (m, 1H), 2.10 (m, 2H), 1.75 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 134.5, 129.3, 128.4, 126.9, 104.2, 88.0, 77.0, 64.9, 61.4, 30.5, 29.6, 29.4, 29.3, 14.1; IR ($CHCl_3$) 3014, 2962, 1731, 1659, 1642, 1484, 1451, 1373, 1357, 1206, 1194, 1145, 887, 786, 693 cm^{-1}; MS (ESI TOF) *m/e* 334.17 $(M + H)^+$. Anal. ($C_{18}H_{23}NO_5$) C, H, N.

***cis*-Ethyl 2-(2-methoxycarbonylcyclopropyl)-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 20a:** 47% yield; white crystals (CH_2Cl_2/hexane); mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.30 (m, 3H), 4.13 (m, 2H), 3.61 (s, 3H), 2.53 (m, 1H), 2.45 (m, 1H), 2.12 (m, 1H), 1.98 (m, 2H), 1.68 (m, 1H), 1.31 (m, 1H), 1.21 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 172.0, 131.6, 129.4, 128.4, 126.9, 89.0, 77.0, 61.7, 51.8, 29.2, 28.9, 25.5, 17.3, 14.0, 11.9; IR ($CHCl_3$) 3028, 3012, 2955, 1727, 1500, 1452, 1439, 1359, 1332, 1266, 1206, 1199, 1178, 1091, 1018, 774, 696 cm^{-1}; MS (ESI TOF) *m/e* 332.15 $(M + H)^+$. Anal. ($C_{18}H_{21}NO_5$) C, H, N.

***trans*-Ethyl 2-(2-methoxycarbonylcyclopropyl)-5-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane-2-carboxylate 20b:** 17% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.28 (m, 3H), 4.24 (m, 2H), 3.58 (s, 3H), 2.66 (dd, J = 14.3, 8.0 Hz, 1H), 2.50 (ddd, J = 14.3, 10.6, 8.2 Hz, 1H), 2.20 (ddd, J = 13.3, 10.6, 8.2 Hz, 1H), 2.01 (ddd, J = 9.0, 8.7, 4.5 Hz, 1H), 1.89 (dd, J = 13.3, 8.2 Hz, 1H), 1.72 (ddd, J = 9.1, 6.7, 4.5 Hz, 1H), 1.27 (t, J = 7.0 Hz, 3H), 1.10 (m, 1H), 0.92 (ddd, J = 8.7, 6.7, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 170.9, 133.9, 129.8, 128.5, 127.2, 88.0, 74.4, 61.6, 51.9, 28.8, 27.9, 26.1, 15.9, 14.2, 11.4; IR ($CHCl_3$) 3021, 2987, 2955, 1728, 1450, 1398, 1370, 1355, 1329, 1199, 1179, 1091, 1021, 891, 705 cm^{-1}; MS (ESI TOF) *m/e* 354.14 $(M + Na)^+$. Anal. ($C_{18}H_{21}NO_5$) C, H, N.

General Procedure for the Reaction of Oxaziridines 14a, 16a, 18a, 20a, 14b, 16b, 18b, and 20b with Iron(II) Sulfate.[18] The desired oxaziridine (250 mg) in absolute ethanol (5 mL) was treated with an equimolar amount of iron(II) sulfate and refluxed for 24 h. The solvent was removed, and the resulting residue was partitioned between water (5 mL) and dichloromethane (15 mL). The water layer was extracted three times more with dichloromethane (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to leave the crude reaction product. Purification was performed using preparative TLC with EtOAc/hexane/acetone as eluent.

Antimalarial Activity. Continuous in vitro cultures of the asexual erythrocytic stage of *P. falciparum* (K1, multidrug-resistant stain) were maintained. Quantitative assessment of antimalarial activity in vitro was determined using the microculture radioisotope technique based on the method described by Desjardins.[19] Effective concentration (EC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of [^{3}H]hypoxanthine by *P. falciparum*.

Antituberculous Activity. Growth inhibitory activity against *Mycobacterium tuberculosis* H37Ra was performed using the microplate Alamar Blue assay (MABA).[20] Standard drugs isoniazid and kanamycin sulfate, the reference compounds for the antimycobacterial assy, showed the minimum inhibitory concentrations (MIC) of 0.040−0.090 and 2.0−5.0 μg/mL, respectively.

Cytotoxicity Assay. The cytotoxicity of oxaziridine analogues against the Vero cell line was evaluated employing the colorimetric method as described by Skehan and co-workers.[21]

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