

SYNTHETIC STUDIES TOWARD HENNOXAZOLE A. USE OF A SELECTIVE BISOXAZOLE ALKYLATION AS THE KEY FRAGMENT COUPLING

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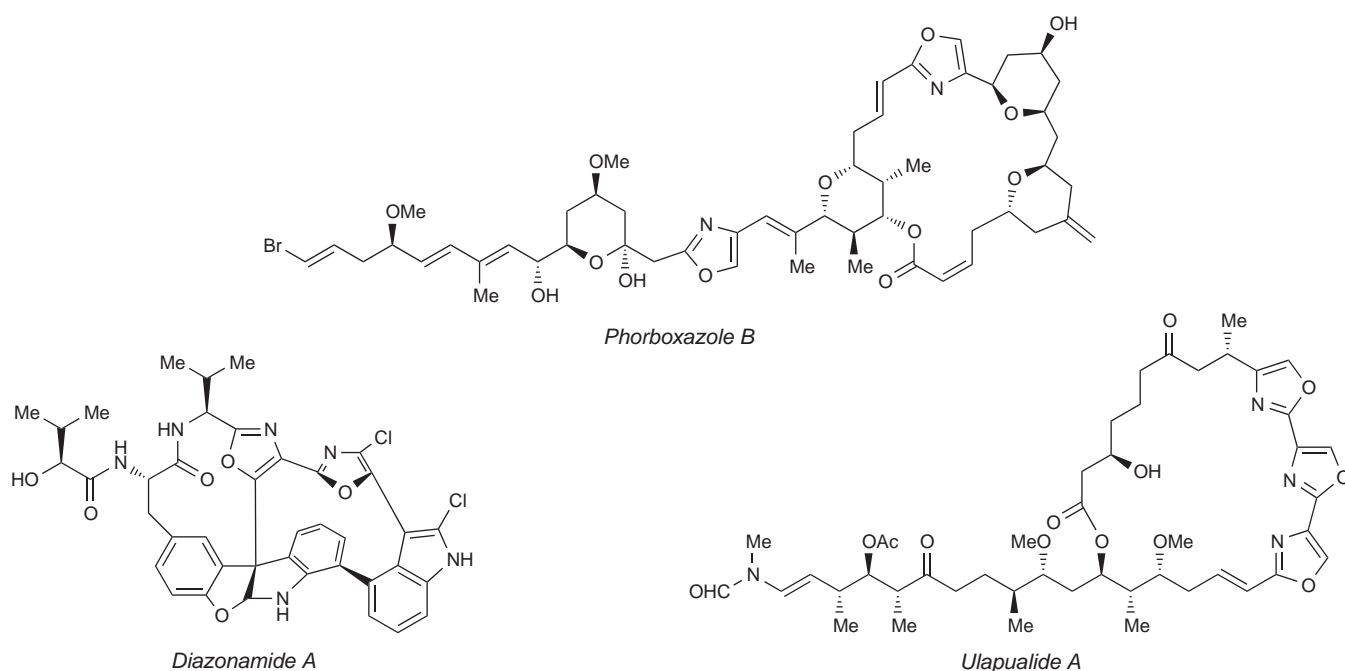
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Abstract – A model system for side chain fragment coupling to the core of hennoxazole A is investigated. Lateral metallation of a C₁₃-TBS-protected bisoxazole, using lithium diethylamide, allows for selective and efficient alkylation at C₁₅.

INTRODUCTION

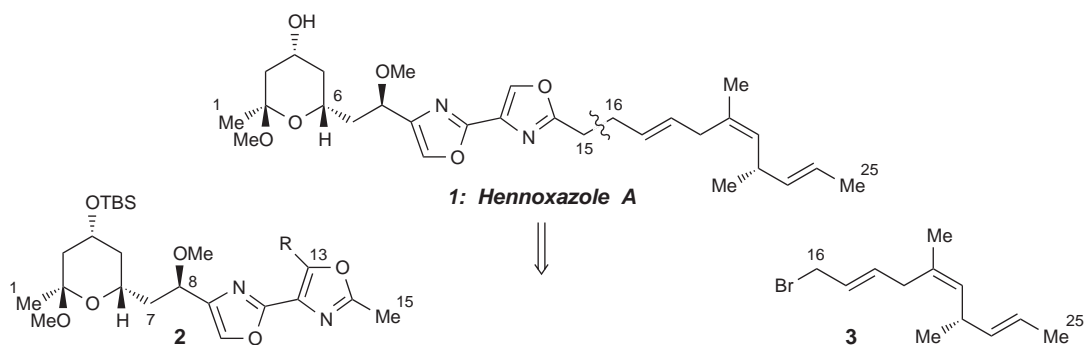
Marine natural products containing the oxazole nucleus have drawn considerable attention recently (Figure 1). Synthetic studies of complex molecules containing isolated 2,4-disubstituted oxazole units such as the phorboxazoles,¹ bisoxazoles such as the hennoxazoles² and diazonamides,³ and trisoxazoles such as the ulapualides,⁴ have contributed methods for the assembly of these systems and have resulted in several total syntheses. The development of relatively mild oxazole-forming reaction sequences⁵ has

Figure 1. Oxazole-Containing Marine Natural Products



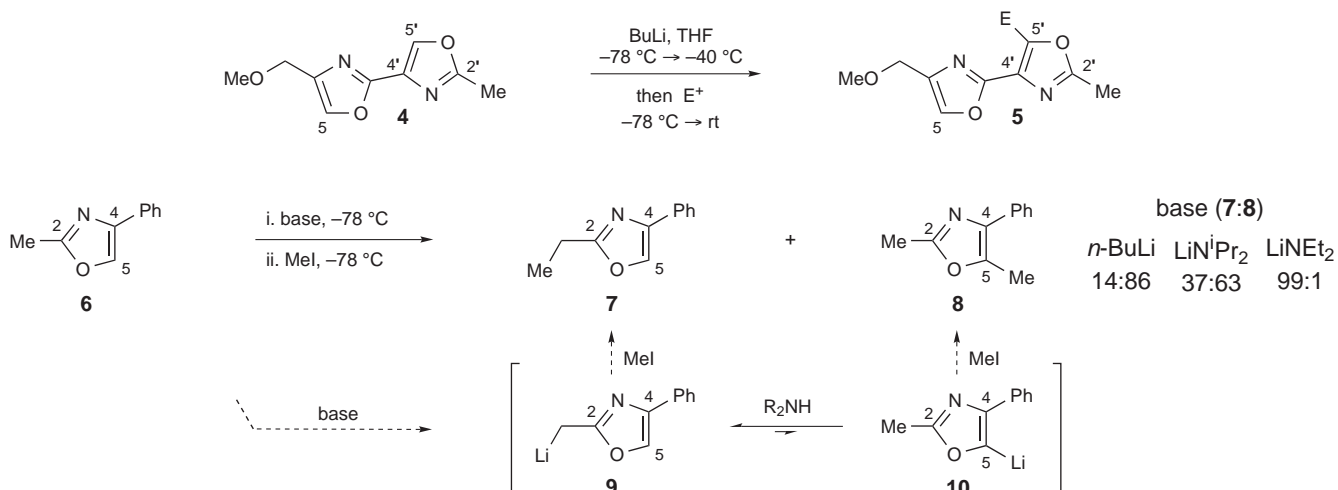
made the late-stage creation of these ring systems a common strategy—with cleavage of an oxazole ring frequently serving as the key disconnection back to major coupling fragments.⁶ Approaches involving end game functionalization of *intact* oxazole rings, however, provide the opportunity to use relatively simple oxazoles as starting materials and then efficiently carry these, practically inert,⁷ heterocycles through a variety of synthetic transformations.⁸ In consideration of these issues, our synthesis plan for hennoxazole A (**1**, Scheme 1) involves late-stage construction of the C₁₅–C₁₆ bond by metallation of a relatively elaborate bisoxazole (**2**) at the C₁₅-methyl position, followed alkylation with an allylic halide C₁₆–C₂₅ side chain fragment (**3**).⁹

Scheme 1. Retrosynthetic Analysis for Hennoxazole A



Synthetically useful lateral metallations of some 2-methyl-oxazole and -thiazole systems have been reported.¹⁰ If these rings are unsubstituted at C₅, however, competitive deprotonation of the C₅-ring hydrogen is frequently observed (Scheme 2).¹¹ In fact, Williams has shown that bisoxazole **4** is lithiated with *n*-BuLi exclusively at the C₅-ring position,¹² suggesting that alkylation of **2** at C₁₅ may be problematic if R = H. Despite this result, previous work confronting a similar problem in the synthesis of phorbazole, demonstrated that the regioselectivity of some oxazole deprotonations can be altered by the use of lithium diethylamide.¹³ As elaborated in the preceding communication,¹⁴ deprotonation of

Scheme 2. Oxazole and Bisoxazole Alkylations



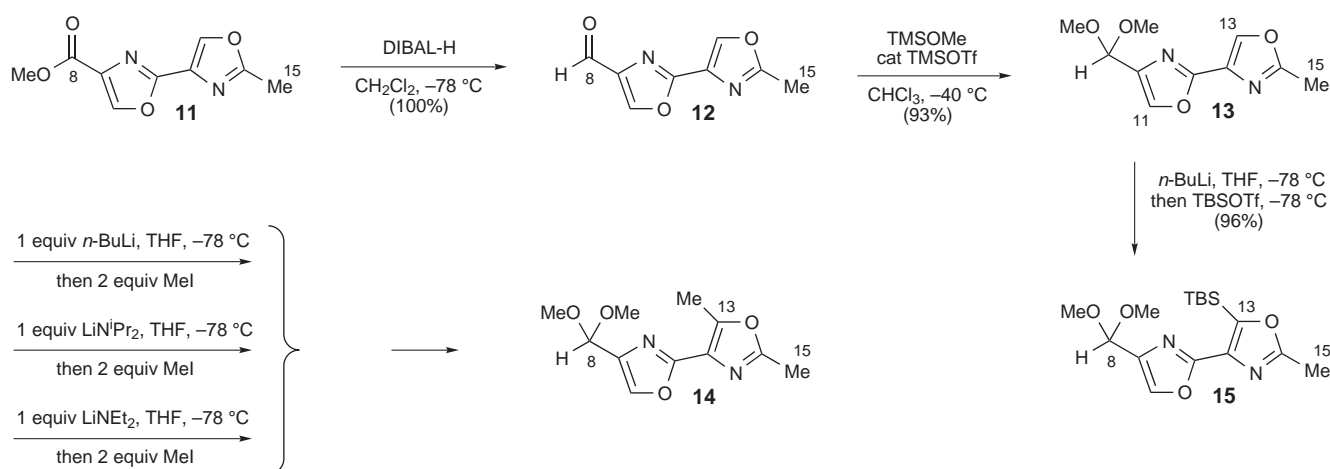
2-methyl-4-phenyloxazole (**6**) using *n*-BuLi at $-78\text{ }^{\circ}\text{C}$ followed by alkylation with methyl iodide gives a 14:86 ratio of products (**7**:**8**) favoring ring methylation, while the use of LiNEt₂ leads to alkylation solely at the C₂-methyl site. This reversal of regioselectivity is thought to arise from the ability of diethylamine to mediate the low-temperature equilibration of a kinetic mixture of otherwise noninterconverting lithiated intermediates (**9** and **10**).¹⁵

Herein we report our results on a model fragment coupling for hennoxazole A using lithium diethylamide.

RESULTS AND DISCUSSION

To test the viability of our key side chain coupling strategy, we first prepared bisoxazole (**13**) as a model substrate (Scheme 3). Bisoxazole ester (**11**)¹⁶ was reduced with DIBAL-H in CH₂Cl₂ at low temperature to give aldehyde (**12**)¹⁷ in quantitative yield. Dimethyl acetal (**13**) was then generated under Noyori conditions¹⁸ in 93% yield. In results consistent with Williams' studies of **4**,¹² treatment of bisoxazole (**13**) with *n*-BuLi led to deprotonation exclusively at the C₁₃ ring position (hennoxazole numbering), with no deprotonation occurring at the C₁₅-methyl group. For this substrate, replacing the base with LDA or LiNEt₂ did not alter the regioselectivity, suggesting that deprotonation at C₁₃ is both kinetically and thermodynamically favored.¹⁹ Attempts to alkylate the dianion of **13** were not fruitful. To circumvent this dilemma, we chose to block C₁₃ with a silyl protecting group.²⁰ Although TMS and TES groups were found to be too labile under these metallation conditions, the TBS group proved to be suitable. Treatment of **13** with *n*-BuLi followed by addition of TBSOTf led to C₁₃-protected bisoxazole (**15**) in 96% yield.

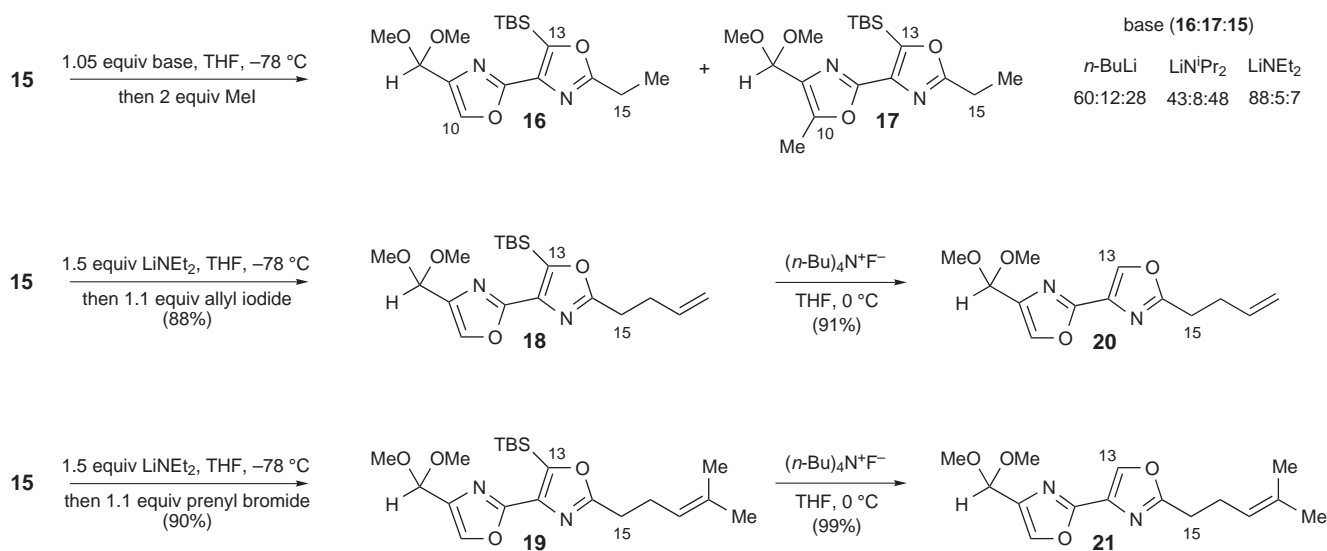
Scheme 3. Preparation of a Hennoxazole Model System



To model our key coupling step, we treated protected bisoxazole (**15**) with several different strong bases and quenched with MeI (Scheme 4). Gratifyingly, alkylation occurred at the desired C₁₅ site, with LiNEt₂ providing the best results. It is interesting to note that *n*-BuLi and LDA both gave poor conversion and small amounts of product **17**—methylated at *both* at the C₁₅-methyl and C₁₀-ring positions—at the

expense of starting material conversion.²¹ No significant monomethylation at C₁₀ was observed. We speculate that this result could potentially arise from rate differences of the C₁₀⁻ and C₁₅⁻ anions with respect to alkylation and intermolecular proton exchange. Chelation of lithium between C₁₀ and an oxygen atom of the C₈-dimethyl acetal could decrease the reactivity at this center and lead to the observed product mixtures. To better mimic the reactivity of the actual side chain fragment (**3**), we also alkylated **15** with allyl iodide and prenyl bromide, both of which gave excellent results with LiNEt₂.²² Finally, treatment of alkylated products (**18**) and (**19**) with TBAF demonstrated that the oxazole could be cleanly deprotected under mild conditions.²³

Scheme 4. Hennoxazole Side Chain Alkylation Model Studies



CONCLUSION

Selective alkylation of a C₈–C₁₅ model for the bisoxazole portion of hennoxazole A is possible using lithium diethylamide when the C₁₃-position is blocked. Thus, modification of our initial retrosynthetic analysis (Scheme 1) to include a silyl protecting group at C₁₃ (R = TBS) should provide a successful fragment coupling approach to hennoxazole A. Further reports on this synthesis will be forthcoming.

ACKNOWLEDGEMENTS

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 21. Product identities and ratios were determined using a combination of ¹H NMR and GCMS analysis. All isolated yields are following silica gel chromatography. Spectral data for **12–15** and **19–21** are given in reference 23.
 22. Representative Bisoxazole Alkylation Procedure using LiNEt₂: To a solution of diethylamine (22 μL, 0.213 mmol) in THF (1 mL) at –78 °C under Ar was added *n*-butyllithium (133 μL of a 1.5 M hexane solution, 0.199 mmol) dropwise. After stirring at –78 °C for 5 min, warming to 0 °C for 10 min, and re-cooling to –78 °C, this solution was added via canula to a solution of bisoxazole (**15**) (48.0 mg, 0.142 mmol) in THF (1 mL). The resulting bright red solution was stirred at –78 °C for 30 min. Allyl iodide (14.3 μL, 0.156 mmol) was added dropwise and the color faded to a light orange. After 15 min, the reaction was quenched with sat. aq. NaHCO₃ (2 mL) and warmed to rt. The resulting mixture was partitioned between CH₂Cl₂ (10 mL) and sat. aq. NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL), the combined organics were dried over a 1:1 mixture of K₂CO₃ and Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel deactivated with 2.5% Et₃N) eluting with 1:4 Et₂O:hexanes to afford the allylated product (**18**, 47.0 mg, 88%) as a colorless oil; ¹H NMR (CDCl₃) δ 7.68 (d, *J* = 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.3, 6.5 Hz, 1H), 5.45 (d, *J* = 0.6 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.99 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.36 (s, 6H), 2.94 (t, *J* = 7.9 Hz, 2H), 2.55 (dt, *J* = 7.1, 7.8 Hz, 2H), 0.93 (s, 9H), 0.376 (s, 6H) ppm.; ¹³C NMR (CDCl₃) δ 168.1, 156.8, 155.0, 139.8, 139.1, 136.7, 136.5, 116.1, 98.8, 53.0, 31.2, 27.7, 26.7, 17.8, –5.7 ppm.; IR (neat) 1062, 1103, 1193, 1251, 1391, 1470, 1580, 1612, 2858, 2931 cm⁻¹; Anal. Calcd for C₁₉H₃₀N₂O₄Si: C, 60.29; H, 7.99; N, 7.40. Found: C, 60.56; H, 8.02; N, 7.37.
 23. Spectral data for other new compounds are as follows:

12: ¹H-NMR (CDCl₃, 300 MHz) δ 10.0 (s, 1H), 8.30 (s, 1H), 8.23 (s, 1H), 2.57 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 184.3, 163.3, 156.6, 143.7, 141.7, 139.6, 129.7, 14.0 ppm.; IR (neat) 3124, 1686, 1295, 1206 cm⁻¹; Anal. Calcd for C₈H₆N₂O₃: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.08; H, 3.45; N, 15.70.

13: ¹H-NMR (CDCl₃, 300 MHz) δ 8.08 (s, 1H), 7.64 (s, 1H), 5.38 (s, 1H), 3.30 (s, 6H), 2.45 (s, 3H) ppm.; ¹³C-NMR (CDCl₃, 75 MHz) δ 162.8, 155.7, 139.7, 138.5, 137.0, 130.6, 98.6, 53.1, 14.0

ppm.; IR (neat) 3119, 1636, 1530, 1305, 1106, 1058, 984 cm^{-1} ; Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.68; H, 5.41; N, 12.41.

14: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.66 (d, $J = 0.8$ Hz, 1H), 5.43 (s, $J = 0.8$ Hz, 1H), 3.35 (s, 6H), 2.60 (s, 3H), 2.43 (s, 3H) ppm.; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 160.3, 156.7, 149.9, 139.5, 136.4, 125.2, 98.7, 53.0, 13.8, 11.7 ppm.; IR (neat) 2937, 1593, 1197, 1097, 1055, 980 cm^{-1} ; Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.57; H, 5.97; N, 11.66.

15: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.69 (d, $J = 0.9$ Hz), 5.45 (d, 1H, $J = 0.9$ Hz), 3.37 (s, 6H), 2.53 (s, 3H), 0.94 (s, 9H), 0.38 (s, 6H) ppm.; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 165.3, 156.8, 155.0, 139.9, 139.2, 136.7, 98.8, 53.0, 26.7, 17.8, 14.0, -5.7 ppm.; IR (neat) 2929, 1611, 1114, 1101, 1061 cm^{-1} ; Anal. Calcd for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_4\text{Si}$: C, 56.78; H, 7.74; N, 8.28. Found: C, 56.98; H, 7.67; N, 8.29.

19: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 7.68 (d, $J = 0.9$ Hz, 1H), 5.45 (d, $J = 0.9$ Hz, 1H), 5.13 (t, $J = 7.1$ Hz, 1H), 3.36 (s, 3H), 2.85 (t, $J = 7.3$ Hz, 2H), 2.4 (dt, $J = 7.4, 7.4$ Hz, 2H), 1.66 (s, 3H), 1.56 (s, 3H), 0.93 (s, 9H), 0.37 (s, 6H) ppm.; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 168.5, 156.9, 154.8, 139.8, 139.1, 136.7, 133.6, 122.4, 98.8, 52.9, 28.5, 26.6, 25.9, 25.8, 17.82, 17.79, -5.7 ppm.; IR (neat) 2954, 2930, 1469, 1251, 1104, 1062, 843, 124 cm^{-1} ; Anal. Calcd for $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_4\text{Si}$: C, 62.03; H, 8.43; N, 6.89. Found: C, 62.17; H, 8.56; N, 6.94.

20: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.17 (s, 1H), 7.71 (d, $J = 1.0$ Hz, 1H), 5.84 (ddt, $J = 17.1, 10.3, 6.5$ Hz, 1H), 5.47 (d, $J = 1.0, 1\text{H}$), 5.08 (ddt, $J = 17.1, 3.2, 1.6$ Hz, 1H), 5.02 (ddt, $J = 10.2, 2.8, 1.2$ Hz, 1H), 3.38 (s, 3H), 2.93 (t, $J = 7.2$ Hz, 2H), 2.58 (dt, $J = 6.6, 6.6$ Hz, 2H) ppm.; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 165.6, 155.8, 139.8, 138.5, 137.1, 136.3, 130.5, 116.4, 98.6, 53.1, 30.1, 27.8 ppm.; IR (neat) 2939, 1103, 1059, 984, 916 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.94; H, 6.16; N, 10.46.

21: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 8.16 (s 1H), 7.70 (d, $J = 0.9$ Hz, 1H), 5.46 (d, $J = 0.8$ Hz, 1H), 5.11 (t, $J = 7.1$ Hz, 1H), 3.74 (s, 6H), 2.83 (t, $J = 7.3$ Hz, 2H), 2.48 (dt, $J = 7.4, 6.8$ Hz, 2H), 1.66 (s, 3H), 1.58 (s, 3H) ppm.; $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 166.0, 155.8, 139.7, 138.4, 137.0, 133.9, 130.4, 122.0, 98.6, 53.0, 28.5, 25.8, 25.7, 17.8 ppm.; IR (neat) 2933, 1103, 1059, 984 cm^{-1} ; Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.38; H, 7.06; N, 9.36.