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Synthesis of alkaloids from aminol derivatives by β-fragmentation of primary alkoxyl radicals

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Abstract—The fragmentation of primary alkoxyl radicals, often described as low yielding and plagued by side reactions, proceeded in good to excellent yields when aminol derivatives were used as substrates. Remarkably, no side reactions such as hydrogen abstraction or oxidation were observed. The fragmentation can be coupled with an alkylation reaction to give 2-substituted pyrrolidine and piperidine rings such as alkaloid analogues and functionalized, chiral nitrogen heterocycles.
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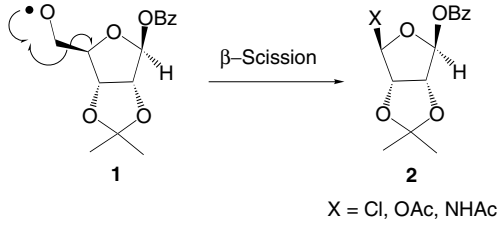
The β-fragmentation of alkoxyl radicals (Scheme 1) can be an efficient method for synthesizing a wide range of compounds, including medium- and large-sized rings, heterocycles and halogenated compounds.[1] For instance, the synthesis of natural products[2] such as deoxyvernolepin,[2a,n] cyclophellitol,[2h,m] rapamycin[2o] and muscone[2p] used a β-scission as the key step. The alkoxyl radicals can be generated from the corresponding alcohols by treatment with reagents such as (diacetoxyiodo)benzene (DIB) and iodine, HgO-iodine or LTA.[1] When tertiary alkoxyl radicals are generated, β-fragmentation is the major or the exclusive pathway. However, the fragmentation of primary alkoxyl radicals is usually plagued by side reactions, such as intramolecular hydrogen abstraction,[3] addition to double bonds[4] or oxidation,[1j] and thus has been scarcely used in synthesis.



Scheme 1. β-Scission in carbohydrates.

In a recent publication, we reported that the fragmentation of primary alkoxyl radicals could proceed in good yields by using carbohydrate substrates[5] **1** (Scheme 1). By controlling the reaction conditions, the stereochemistry of the substituents and the protecting groups, the β-fragmentation was made to predominate over the side reactions. This proved to be a direct route to polyols and α,ω-differently substituted cyclic ethers **2**.

These results suggested that the β-fragmentation of primary alkoxyl radicals could be synthetically useful with appropriate substrates. The alkoxyl radicals generated from aminol derivatives **3** (Scheme 2) seemed particularly promising. Many aminol derivatives are commercial products or are readily obtained therefrom. Moreover, highly functionalized aminols can be synthesized from sugars and other chiral materials. If the β-scission takes place, different nitrogen heterocycles **4** might be easily obtained.

A variety of substituents could be introduced at the 2-position. In effect, the *C*-radical **5** resulting from the fragmentation would probably be oxidized by excess reagent to an acyliminium ion **6**, which could be trapped by different carbon or heteroatom nucleophiles.[6] The resulting 2-substituted heterocycles **4** are present in alkaloids,[7a] chiral auxiliaries[7b,c] and synthetic drugs.[7d,e]

However, the alkoxyl radical **3** could also give undesired reactions, such as hydrogen abstraction. The distance

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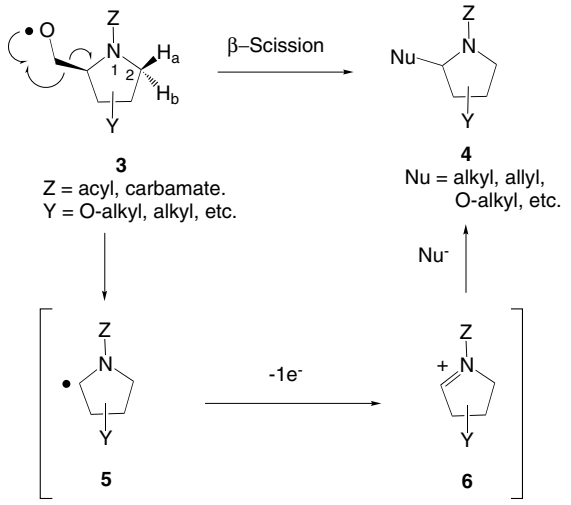
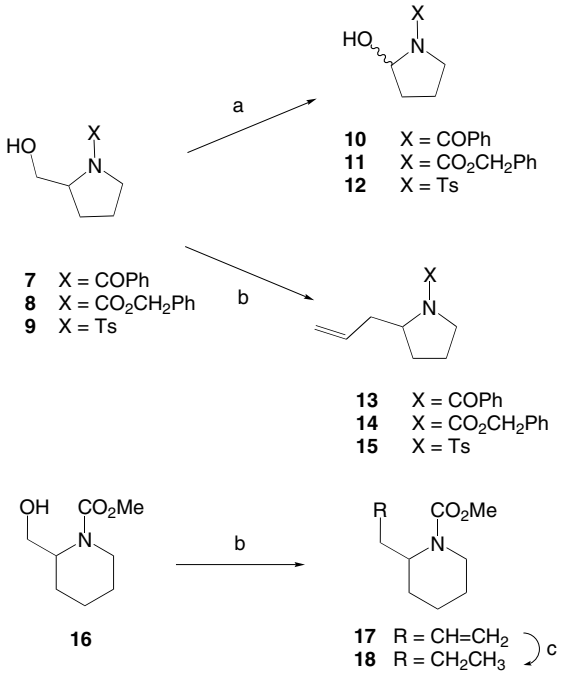


Scheme 2. β-Scission in aminol derivatives.

between 2-H_a and the alkoxyl radical lies in the 2.3–2.8 Å range where H-abstraction is favored. Whether the scission or the abstraction would predominate had yet to be determined.

In order to study the possible competition between β-scission and other feasible reactions, different aminol derivatives **7**–**9** (Scheme 3) were prepared in good yields by acylation or sulfonylation of commercial precursors. When substrates **7**–**9** were treated with DIB and iodine at room temperature (Table 1, entries 1–3), the scission products **10**–**12** were isolated in good yields. To our satisfaction, no products derived from intramolecular hydrogen abstraction or oxidation were detected. These results suggested that the fragmentation was much faster than H-abstraction. Although the scission is a reversible reaction, a rapid oxidation of the *C*-radical to an acyliminium ion would render the whole process irreversible.

The addition of carbon nucleophiles to the acyliminium intermediate was studied next. After treatment of compounds **7**–**9** with DIB-iodine for 2.5 h, the reaction



Scheme 3. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, rt, then H_2O; (b) DIB, I_2, CH_2Cl_2, rt, then 0 °C, AllylTMS and $BF_3{\cdot}Et_2O$; (c) H_2, Pd/C, EtOAc, 99%.

mixture was cooled to 0 °C and allyltrimethylsilane and $BF_3{\cdot}OEt_2$ were added (entries 4–6), affording the desired allylpyrrolidines **13**–**15** in good to excellent yields.

This one-pot fragmentation–allylation reaction was then used to synthesize a precursor of the alkaloid coniine, which is the active principle of hemlock poison.[8] Thus, when the piperidine derivative **16** was treated under the previous conditions (entry 7), the volatile allyl derivative **17** was isolated in moderate yield. This derivative has been previously transformed by us[8a] into the coniine methyl carbamate **18**, in quantitative yield.

The scission of pyroglutamol **19** (Scheme 4) was studied in order to determine whether the formation of a nitro-

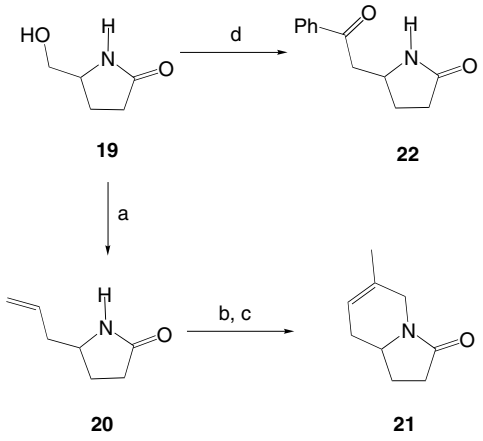
Table 1. One-pot β-fragmentation of aminol derivatives—oxidation–nucleophilic addition[a,b]

Entry	Substrate	Nucleophile	Products (%)[c]	Scission overall yield (%)
1	**7**	H_2O[a]	**10** (66)	66
2	**8**	H_2O[a]	**11** (67)	67
3	**9**	H_2O[a]	**12** (64)	64
4	**7**	AllylTMS[b]	**10** (4), **13** (91)	95
5	**8**	AllylTMS[b]	**11** (10), **14** (76)	86
6	**9**	AllylTMS[b]	**12** (5), **15** (86)	91
7	**16**	AllylTMS[b]	**17** (52)	52
8	**19**	AllylTMS[b]	**20** (85)	85
9	**19**	PhC(OTMS)=CH_2[b]	**22** (73)	73
10	**23**	AllylTMS[b]	**24** (41), **25** (23), **26** (22)	86
11	**23**	PhC(OTMS)=CH_2[b]	**27** (64)	64

[a] The aminol derivative (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature under nitrogen for 2.5 h. After that time, it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] The aminol derivative (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and stirred at room temperature under nitrogen for 2.5 h. After that time, it was cooled to 0 °C and $BF_3{\cdot}Et_2O$ (2 equiv) and an excess of the nucleophile (5 equiv) were added. The reaction was allowed to reach rt and stirred for 4 h, then it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[c] The yields are given for products purified by chromatography on silica gel.



Scheme 4. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, rt, then 0 °C, AllylTMS and $BF_3{\cdot}Et_2O$; (b) NaH, DMF, 0 °C, then $ClCH_2$–C(Me)=CH_2, 64%; (c) Grubbs' catalyst, CH_2Cl_2, 95%; (d) DIB, I_2, CH_2Cl_2, rt, then 0 °C, PhC(OTMS)=CH_2 and $BF_3{\cdot}Et_2O$.

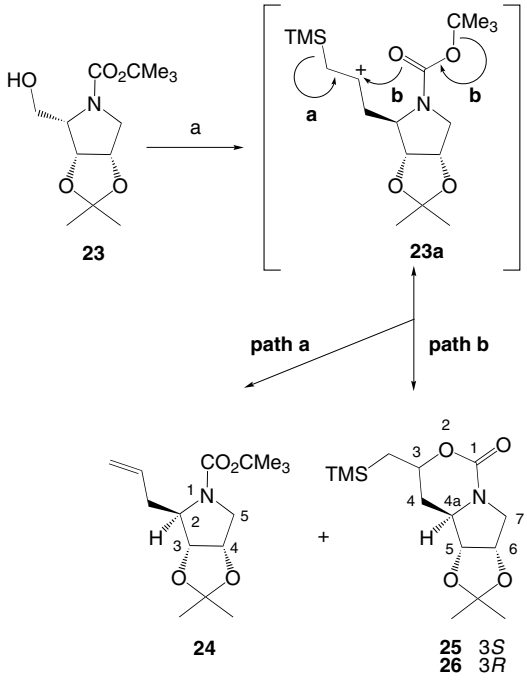
gen radical would compete with the formation of the primary alkoxyl radical. Rewardingly, the formation and scission of the alkoxyl radical were the main reactions, and the allylation product **20** was obtained in 85% yield (entry 8). This allyl derivative was transformed into the indolizidine alkaloid analogue **21** in two steps. Many indolizidine alkaloids are glycosidase enzyme inhibitors, and exhibit antiviral or antitumour activities.[9]

The addition of other carbon nucleophiles, such as enol silyl ethers, was also studied. When pyroglutamol **19** was treated with DIB-iodine followed by the addition of phenyl(trimethylsilyloxy)ethene and a Lewis acid, the phenyl ketone **22** was formed in good yield (entry 9). The formation of ketone **22**, a sedamine alkaloid analogue,[7a] highlights the versatility of this methodology.

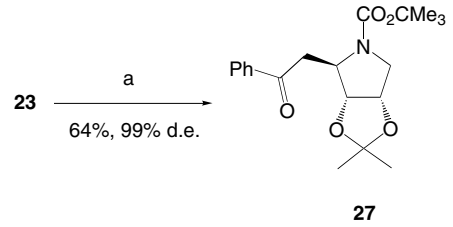
Since many substrates for the fragmentation–alkylation reaction can be easily prepared from sugars and other chiral materials, this methodology could afford a wide range of functionalized, chiral nitrogen heterocycles. For instance, the iminosugar **23** was easily prepared from commercially available ribonolactone.[10] When the scission–alkylation reaction (Scheme 5) was carried out using allyltrimethylsilane as the nucleophile (entry 10), the allyl derivative **24** and two lactones **25** and **26** were obtained,[11–13] in 86% overall yield.

The three products derive from the same intermediate **23a**, formed by addition of the nucleophile from the less hindered face. The intermediate evolved either by loss of the TMS group (path a) to give **24**, or by nucleophilic addition of the carbamate oxygen and concomitant loss of the *tert*-butyl group,[14] (path b) to give the lactones **25** and **26**. Since the TMS group can be replaced by a hydroxyl group,[15] a dioxygenated chain may be easily obtained.

When phenyl(trimethylsilyloxy)ethene was used as a nucleophile (entry 11), the alkylation proceeded with high stereoselectivity, affording exclusively the 2*R* phenyl ketone **27**[16] (Scheme 6). This fragmentation–alkylation reaction also took place in good yield, and no side-reactions were detected.



Scheme 5. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, rt, then 0 °C, AllylTMS and $BF_3{\cdot}Et_2O$.



Scheme 6. Reagents and conditions: (a) DIB, I_2, CH_2Cl_2, rt, hν, then 0 °C, PhC(OTMS)=CH_2 and $BF_3{\cdot}Et_2O$.

In summary, the fragmentation of primary alkoxyl radicals proceeded in good to excellent yields when aminol derivatives were used as substrates. Remarkably, no side-reactions such as hydrogen abstraction or oxidation were observed. The fragmentation can be coupled with an alkylation reaction, and thus, a hydroxymethyl group can be replaced in one step by a more complex lateral chain. The application of this methodology to the synthesis of 2-substituted pyrrolidine and piperidine rings, such as alkaloid analogues and functionalized, chiral nitrogen heterocycles has been illustrated.

Acknowledgements

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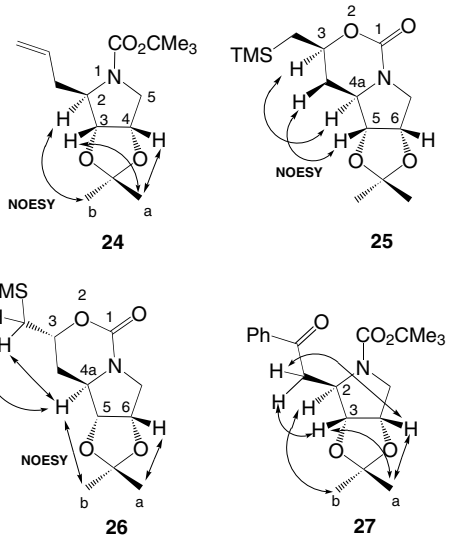
11. All the compounds were completely characterized by ^{1}H and ^{13}C NMR, MS, HRMS, IR and elemental analysis. 2D-COSY, HSQC and NOESY experiments were also carried out. Selected NMR and MS data for compounds **24–26**: (a) Compound **24**: ^{1}H NMR (500 MHz, $CDCl_3$, 70 °C) δ 1.30 (3H, s, Me_aMe$_b$C), 1.46 (3H, s, Me$_a$$Me_b$C), 1.47 (9H, s, Me_3C), 2.21 (1H, ddd, $J = 7.7, 7.7, 15.1$ Hz, CH_aH$_b$–CH=CH$_2$), 2.31 (1H, m, CH$_a$$H_b$–CH=CH$_2$), 3.33 (1H, dd, $J = 5.2, 13.0$ Hz, 5-H$_a$), 3.81 (1H, d, $J = 13.0$ Hz, 5-H$_b$), 4.10 (1H, m, 2-H; at 26 °C dd, $J = 5.8, 6.4$ Hz), 4.45 (1H, d, $J = 5.9$ Hz, 3-H), 4.66 (1H, dd, $J = 5.4, 5.5$ Hz, 4-H), 5.09 (1H, dd, $J = 1.5, 9.3$ Hz, =CH_aH$_b$), 5.11 (1H, dd, $J = 1.0, 18.3$ Hz, =CH$_a$$H_b$), 5.76 (1H, dddd, $J = 7.0, 7.1, 10.4, 17.2$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$, 26 °C). Mixture of two rotamers: δ 25.0 (CH$_3$), 26.9 (CH$_3$), 28.4 (3×CH$_3$), 35.3/36.0 (CH$_2$), 51.4/52.0 (CH$_2$), 62.6/63.1 (CH), 78.6/79.3 (CH), 79.7 (C), 83.2/84.0 (CH), 111.6 (C), 118.2 (CH$_2$), 133.8 (CH), 154.3 (C); MS m/z (rel intensity) 283 (M^+, <1), 142 ($M^+ + H–C_3H_5–CO_2CMe_3$, 100); Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.60; H, 8.86; N, 4.78. (b) Compound **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (9H, s, Me_3Si), 0.94 (1H, dd, $J = 7.7, 14.5$ Hz, CH_aH$_b$ TMS), 1.17 (1H, dd, $J = 6.8, 14.5$ Hz, CH$_a$$H_b$TMS), 1.34 (3H, s, Me_aMe$_b$C), 1.40 (1H, ddd, $J = 11.4, 11.5, 13.4$ Hz, 4-H$_a$), 1.53 (3H, s, Me$_a$$Me_b$C), 2.31 (1H, ddd, $J = 2.0, 4.6, 13.5$ Hz, 4-H$_b$), 3.46 (1H, dd, $J = 2.3, 13.3$ Hz, 7-H$_a$), 3.51 (1H, ddd, $J = 5.1, 6.4, 11.5$ Hz, 4a-H), 4.18 (1H, dd, $J = 6.4, 13.2$ Hz, 7-H$_b$), 4.24 (1H, dd, $J = 6.3, 6.3$ Hz, 5-H), 4.36 (1H, dddd, $J = 1.9, 6.8, 7.0, 12.8$ Hz, 3-H), 4.75 (1H, ddd, $J = 2.5, 6.3, 6.3$ Hz, 6-H); ^{13} C NMR (100.6 MHz, $CDCl_3$) δ –0.9 (3×CH$_3$), 24.4 (CH$_2$), 25.5 (CH$_3$), 27.7 (CH$_3$), 34.7 (CH$_2$), 50.3 (CH$_2$), 60.9 (CH), 76.0 (CH), 77.6 (CH), 84.4 (CH), 113.8 (C), 152.2 (C); MS m/z (rel intensity) 299 (M^+, 1), 284 (M^+–CH_3, 31), 73 (TMS, 100); Anal. Calcd for $C_{14}H_{25}NO_4Si$: C, 56.16; H, 8.42; N, 4.68. Found: C, 56.08; H, 8.77; N, 4.68. (c) Compound **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (9H, s, Me_3Si), 0.88 (1H, dd, $J = 7.0, 14.5$ Hz, CH_aH$_b$TMS), 1.21 (1H, dd, $J = 8.8, 14.6$ Hz, CH$_a$$H_b$TMS), 1.36 (3H, s, Me_aMe$_b$C), 1.55 (3H, s, Me$_a$$Me_b$C), 1.81 (1H, ddd, $J = 4.7, 11.2, 13.4$ Hz, 4-H$_a$),

2.15 (1H, ddd, $J = 2.2$, 4.9, 13.5 Hz, 4-H_b), 3.49 (1H, dd, $J = 2.2$, 13.2 Hz, 7-H_a), 3.58 (1H, ddd, $J = 5.5$, 5.7, 11 Hz, 4a-H), 4.21 (1H, dd, $J = 6.4$, 13.3 Hz, 7-H_b), 4.28 (1H, dd, $J = 6.4$, 6.4 Hz, 5-H), 4.61 (1H, m, 3-H), 4.75 (1H, ddd, $J = 2.3$, 6.2, 6.2 Hz, 6-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −1.1 (3×CH_3), 22.5 (CH_2), 25.5 (CH_3), 27.7 (CH_3), 31.8 (CH_2), 50.4 (CH_2), 57.1 (CH), 74.8 (CH), 77.4 (CH), 84.6 (CH), 113.9 (C), 151.6 (C); MS m/z (rel intensity) 284 (M^+-CH_3, 16), 73 (TMS, 100); Anal. Calcd for $C_{14}H_{25}NO_4Si$: C, 56.16; H, 8.42; N, 4.68. Found: C, 56.11; H, 8.48; N, 4.77.

12. Theoretical coupling constants were calculated over the minimized structures for all possible isomers, by using the Karplus–Altona equation implemented in the Macromodel 7.0 program. See: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792, The calculated constants are in good agreement with the experimental ones.
13. The assigned stereochemistries were also supported by NOESY experiments (see bottom drawing). Compound **24**: Spatial correlations were observed for 2-H (δ_H 4.10)/Me_b (δ_H 1.46), and for 3-H (δ_H 4.45)/Me_a (δ_H 1.30)/4-H (δ_H 4.66); Compound **25**: Spatial interactions were observed for: 3-H (δ_H 4.36)/4a-H (δ_H 3.51) and for 4-H_a (δ_H 1.40)/5-H (δ_H 4.24); Compound **26**: Spatial interactions were observed for: CH_2TMS (δ_H 1.21 and 0.88)/4a-H (δ_H 3.58), for 4a-H (δ_H 3.58)/Me_b (δ_H 1.55), and for 6-H (δ_H 4.75)/Me_a(δ_H 1.36).
14. Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724.
15. (a) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth. Coll.* **1993**, *VIII*, 315; (b) See also: Dikshit, D. K.; Goswami, L. N.; Singh, V. S. *Synlett* **2003**, 1737–1739, and references cited therein.
16. (a) Selected NMR and MS data for Compound **27**: ^{1}H NMR (500 MHz, $CDCl_3$, 26 °C) 1:1 mixture of two rotamers A:B δ 1.30 (3H, s, $Me_a$$Me_b$C), 1.41/1.42 (9H, s/s, Me_3C), 1.45 (3H, s, $Me_a$$Me_b$C), 3.18 (1H, m, C$H_a$$H_b$COPh), 3.29/3.44 (1H, rotamer A: dd, $J = 3.4$, 16.6 Hz/rotamer B: dd, $J = 7.3$, 16.9 Hz, $CH_a$$H_b$COPh), 3.45/3.50 (1H, dd, $J = 5.2$, 12.9 Hz/dd, $J = 5.2$ Hz, 12.6 Hz, 5-H_a), 3.71/3.91 (1H, d, $J = 12.6$ Hz/d, $J = 12.9$ Hz, 5-H_b), 4.43 (1H, m, 2-H; at 70 °C appears as dd, $J = 5.7$, 6.1 Hz), 4.61/4.70 (1H, d, $J = 5.9$ Hz/d, $J = 6.0$ Hz, 3-H), 4.82/4.87 (1H, dd, $J = 5.4$, 5.4 Hz/dd, $J = 5.5$, 5.4 Hz, 4-H), 7.44/7.46 (2H, dd, $J = 7.6$, 7.7 Hz/dd, $J = 7.6$, 7.6 Hz), 7.55/7.57 (1H, dd, $J = 5.6$, 7.4 Hz/dd, $J = 6.6$, 7.4 Hz), 7.94/7.96 (2H, d, $J = 7.0$ Hz/d, $J = 7.2$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) Mixture of two rotamers: δ 24.8 (CH_3), 26.9 (CH_3), 28.3 (3×CH_3), 39.4/40.1 (CH_2), 51.7/52.8 (CH_2), 60.85 (CH), 78.8/79.6 (CH), 79.8/80.1 (C), 83.9/84.7 (CH), 111.6 (C), 128.2 (2×CH), 128.6/128.7 (2×CH), 133.3/133.5 (CH), 136.6 (C), 153.8/154.1 (C), 197.6/198.6 (C); MS m/z (rel intensity) 361 (M^+, 3), 186 (M^++H–C_8H_7O–CMe_3, 100); Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.26; H, 7.92; N, 3.67. (b) The assigned stereochemistry was also supported by NOESY experiments. Spatial correlations were observed for 2-H (δ_H 4.43) and Me_b (δ_H 1.45), for C$H_a$$H_b$COPh ($\delta_H$ 3.18)/3-H (δ_H 4.70), for 3-H (δ_H 4.70)/Me_a (δ_H 1.30)/4-H (δ_H 4.82), and for 4-H (δ_H 4.82)/$CH_a$$H_b$ COPh (δ_H 3.44).



24 **25** **26** **27**