Synthesis and Dehydrobromination of α-Bromo Aldehyde and Ketone Nitroxyl Radical Spin Labels

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Various types of α-bromo aldehyde and ketone derivatives of nitroxyl radicals can be prepared in a selective bromination reaction with pyrrolidone hydrotribromide in the presence of a double bond. The saturated α-bromo aldehydes are dehydrobrominated with 1,8-diazabicyclo [5,4,0]undec-7-ene.

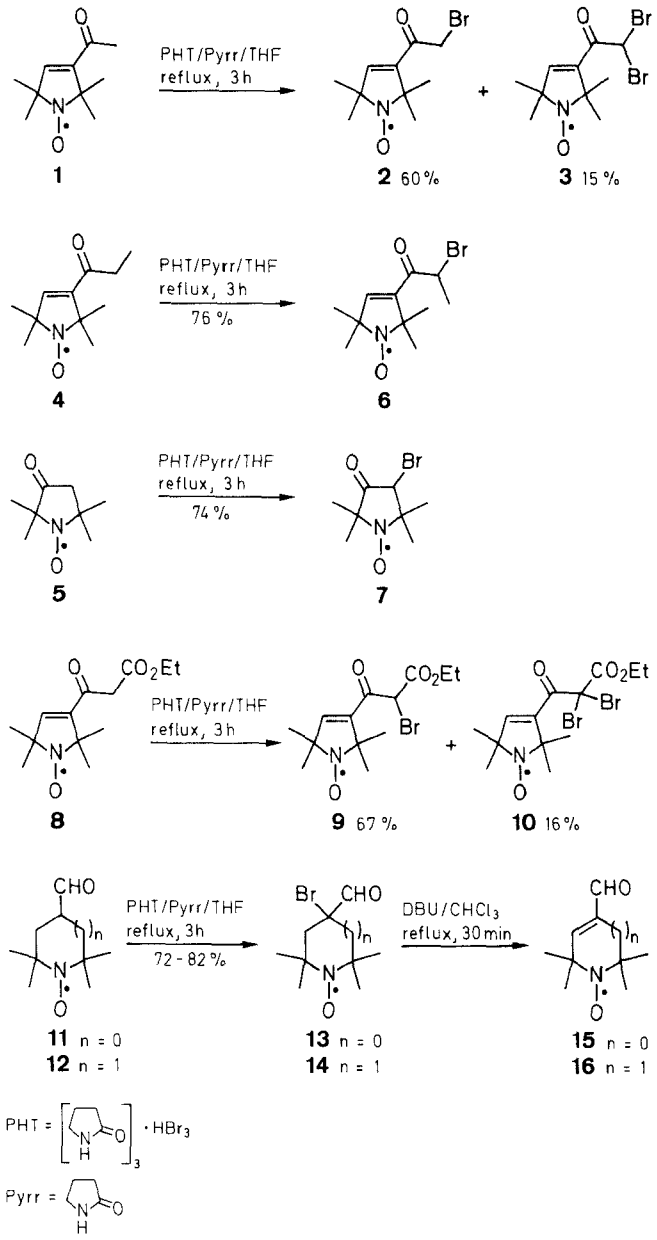
Several reagents are known for the preparation of α-bromo carbonyl compounds.[1-3] The choice is influenced considerably by the selectivity of the attack by the brominating reagent on the substrate molecule, the convenience of the reaction, and the price of the reagent. Although the unusual stability of free nitroxyl radicals allows the utilization of most conventional chemical transformations without an irreversible involvement of the *N*-oxyl function, in the case of bromination reactions the presence of other sensitive functions may influence the choice of reagent.

This was the case as we needed a paramagnetic α-bromo ketone, 3-(bromoacetyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxy radical (**2**), for spin labelling of *cis*-aconitase[4] on its SH group. The preparation of this very convenient spin label reagent,[5] which we believe is a potential alternative SH reagent to the familiar α-haloacetamido nitroxide reagents,[6-8] from 3-acetyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxy radical (**1**) by the copper(II) bromide method[9] gave **2** in very moderate yield (14%). This and our interest in the development of novel bifunctional reagents prompted us to seek more suitable reagents.

The bromination of **1** with 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (dibromo Meldrum's acid),[10] which has been used for the preparation of α-bromo carbonyl compounds,[11,12] resulted in the formation of a dibromo derivative together with the unreacted ketone. Pyrrolidone hydrotribromide (PHT) selectively monobrominates the methyl group of (*E*)-4-phenyl-3-buten-2-one.[13] This reagent proved to be a far better choice for the preparation of **2**, even though some dibromo ketone **3** is also formed in the reaction.

While the bromination of the active methylene group of ketones **4**[5,14] and **5**[15] led to monobrominated ketones **6** and **7** respectively, only the reaction of an α,β-unsaturated ketoester **8**[14] gave again both mono and dibromo unsaturated ketoesters **9** and **10**. The aldehydes **11**[16] and **12**[17] reacted with pyrrolidone hydrotribromide selectively to give α-bromo aldehydes **13** and **14** respectively, and dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[18] allowed easy access to unsaturated aldehydes **15** and **16** which were identical with specimens prepared by other routes[16,19] (Scheme **A**).

The conjugate addition of cyanide to the α,β-unsaturated ester **17**[15] led to the *cis*/*trans* β-cyano esters **18** with predominant formation of the *trans* isomer **18**.

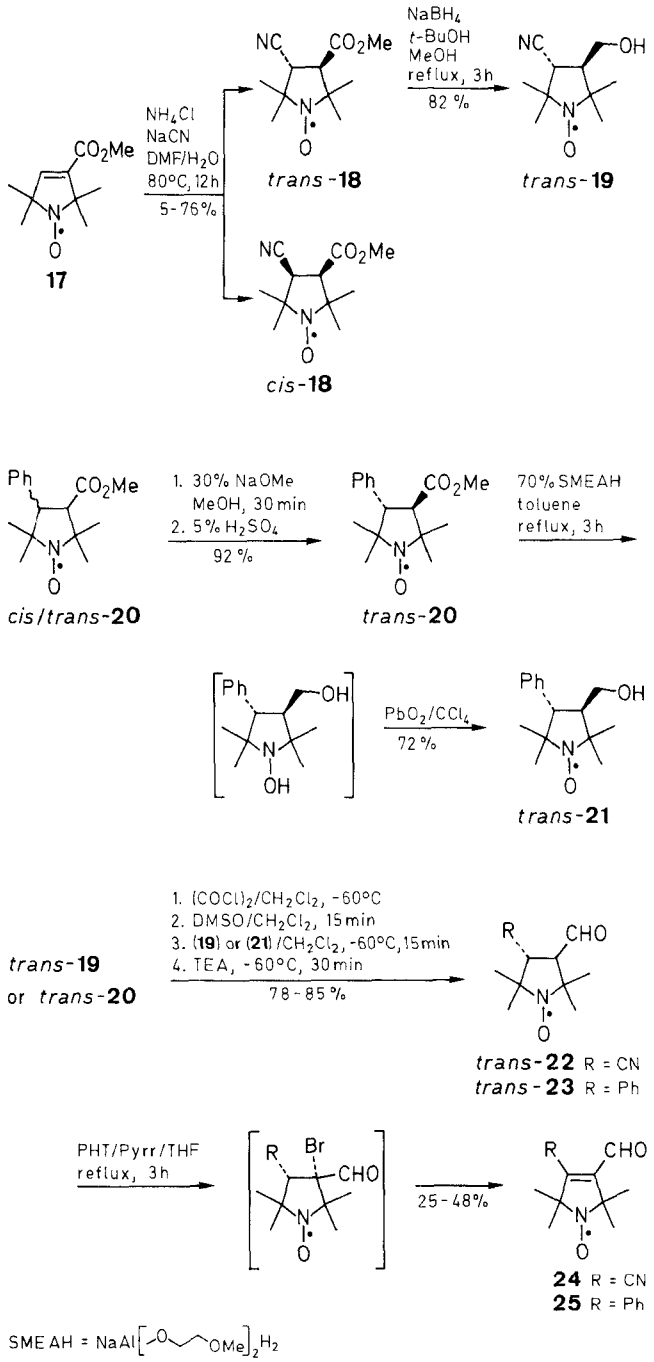


Scheme **A**

Selective reduction of the ester function with sodium borohydride[20] yielded the alcohol **19**, Swern oxidation[16,21] of which gave the β-cyano aldehyde **22**. Reduction of the β-phenyl ester **20**[22] with sodium bis(2-methoxyethoxy)aluminum dihydride (SMEAH)[23] led to the *trans*-alcohol **21** obtained via reoxidation of the labile diamagnetic *N*-hydroxy compound when aerated at room temperature in the presence of lead oxide. The *trans*-β-phenyl alcohol **21** is formed either starting from a mixture of *cis*/*trans* stereoisomers **20** or *trans* isomer **20**, which can be obtained when the isomer mixture is deprotonated with sodium methoxide, then reproton-

ated on acidification. However in the reoxidation reaction of the *N*-hydroxy compound to **21**, the saturated *trans* aldehyde **23** and a very small amount of the α,β-unsaturated aldehyde **25** are also formed. The oxidation of the saturated alcohol **21** with active manganese dioxide[24,25] and lead dioxide in boiling carbon tetrachloride gave a higher yield of aldehyde **25**, but a substantial amount of alcohol **21** remained unreacted. The complete oxidation of **21** to **23** could be achieved only by Swern oxidation (Scheme **B**).

Bromination of these aldehydes **22** and **23** proceeds via α-bromo aldehydes with an active β-hydrogen, which favors elimination of hydrogen bromide during the bromination reaction to give unsaturated aldehydes **24** and **25**, respectively.



Scheme **B**

In summary, bromination with PHT permits the preparation of α-bromo aldehydes and ketones, which may serve as useful multifunctional reagents in place of bromine in nucleophilic substitution or dehydrobromination reactions for the synthesis of α,β-unsaturated aldehydes.

Melting points were measured with a Boetius micro mp apparatus and are not corrected. The IR spectra were recorded on a Zeiss Specord 75 instrument. The mass spectra were recorded with a Finnigan MAT 8430 spectrometer. The ESR spectra of 10^{-4} molar solutions in $CHCl_3$ were obtained on a Zeiss ER-9 spectrometer. All radicals exhibit 3-line spectra characteristic of nitroxide monoradicals. The ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-12 instrument. To obtain high-resolution spectra of the radicals, the sample was reduced with an excess of codissolved PhNHNHPh additive, as described earlier.[22]

Flash column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040–0.063 mm). Preparative TLC was performed on Merck Kieselgel 60 GF_{254} plates (20 × 20 × 0.2 cm). All solvents were of reagent grade. THF and toluene were distilled from SMEAH (Merck).

The analytical and spectral data of all compounds prepared are assembled in the Table.

α-Bromination of Carbonyl Compounds; 3-(Bromoacetyl)-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxy Radical (2); Typical Procedure:

To a stirred solution of **1** (564 mg, 3 mmol) in dry THF (20 mL), 2-pyrrolidinone (300 mg, 3.5 mmol) and PHT (1.73 g, 3.5 mmol) are added. The mixture is refluxed for 3 h, then cooled and filtered. The filtrate is evaporated to dryness and dissolved in Et_2O (20 mL). The ethereal solution is washed with water, (20 mL) dried (Na_2SO_4), and flash chromatographed on silica gel with hexane/EtOAc (2:1). The first yellow band is the dibromo ketone **3**; yield: 135 mg (15%). The second band is the major product monobromo ketone **2**; yield: 468 mg (60%); mp 64–65°C.

Dehydrobromination of α-Bromo Aldehydes with DBU; 3-Formyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-1-yloxy Radical; Typical Procedure:

To a solution of the α-bromo ketone **13** (249 mg, 1 mmol) in dry $CHCl_3$ (20 mL), DBU (167 mg, 1.1 mmol) is added and the mixture is refluxed for 30 min. The cooled mixture is washed with 5% aq. H_2SO_4 and then with water, dried ($MgSO_4$), and evaporated to dryness. The crude unsaturated aldehyde **15** is purified on a preparative silica gel plate with hexane/EtOAc (2:1) as eluent, to give unsaturated aldehyde **15**; yield: 131 mg (78%); mp 78–79°C; Lit.[16] mp 78–79°C.

***cis*- and *trans*-4-Cyano-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy Radical (18):**

To a stirred solution of radical **17** (3.96 g, 20 mmol) in 50% aq. DMF (20 mL), NaCN (735 mg, 15 mmol) and NH_4Cl (802 mg, 15 mmol) are added in a well-ventillated hood (***Caution*** cyanide!) and the mixture is heated at 80°C for 12 h. The cooled mixture is diluted with EtOAc (60 mL), washed with brine (50 mL), dried ($MgSO_4$), and evaporated to dryness. The yellow residue is purified by flash chromatography (hexane/EtOAc, 5:1). The two isomers are separated by chromatography on silica gel to give the *trans*-isomer **18** in the first band as the major yellow crystalline product; yield: 3.42 g (76%); mp 99–100°C (Et_2O/hexane).

^{1}H-NMR ($CDCl_3$/TMS) + PhNHNHPh additive: δ = 0.92 (s, 3 H, CH_3); 1.20 (s, 6 H, $2CH_3$); 1.28 (s, 3 H, CH_3); 2.90 (d, 1 H, J = 12.0 Hz, H-3); 3.10 (d, 1 H, J = 12.0 Hz, H-4); 3.54 (s, 3 H, OCH_3).

The second yellow band is that of the minor *cis* isomer **18**; thick oil; yield: 225 mg (5%).

^{1}H-NMR ($CDCl_3$/TMS) + PhNHNHPh additive: δ = 1.16, 1.26, 1.28, 1.46 (4 s, 3 H each, CH_3), 2.83 (d, 1 H, J = 8.4 Hz, H-3), 2.99 (d, 1 H, J = 8.4 Hz, H-4), 3.70 (s, 3 H, CO_2CH_3).

Table. Physical and Spectroscopic Data of Nitroxyl Radicals Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (neat/KBr) ν(cm^{-1})	MS[b] m/z (%)
2	60	64–65	$C_{10}H_{15}BrNO_2$ (261.1)	1660	260/262 (M^+, 11, 11), 230, 232 (*b*, 10, 10), 151 (*d*, 100), 137 (*b*-CH_2Br, 30), 109 (*b*-$COCH_2Br$, 74)
3	15	124–125	$C_{10}H_{14}Br_2NO_2$ (340.0)	1690	338, 340, 342 (M^+, 9, 17, q), 308, 310, 312 (*b*, 5, 9, 4), 229, 231 (*d*, 60, 59), 167 ($M^+ - CHBr_2$, 19), 137 (*b*-$CHBr_2$, 68), 109 (*b*-$COCHBr_2$, 100)
6	76	98–100	$C_{11}H_{17}BrNO_2$ (275.2)	1655	274, 276 (M^+, 13, 13), 244, 246 (*b*, 14, 14), 229, 231 (*e*, 7, 7), 165 (*d*, 95), 137 (*b*-$CHBrCH_3$, 60), 109 (*b*-$COCHBrCH_3$, 100)
7	74	oil	$C_8H_{13}BrNO_2$ (235.1)	1760	234, 236 (M^+, 5, 5), 220, 222 ($M + H - CH_3$, 5, 5)[c], 204, 206 (*b*, 2, 2), 125 (*d*, 28), 83 ($C_5H_7O^+$, 34)[d], 70 ($C_4H_6O^+$, 100)[d]
9	67	73–74	$C_{13}H_{19}BrNO_4$ (333.2)	1750, 1670	332, 334 (M^+, 14, 14), 223 (*d*, 86), 177 (*d*-EtOH, 100), 109 (*b*-$COCHBrCO_2Et$, 73)
10	16	116–118	$C_{13}H_{18}Br_2NO_4$ (412.1)	1750, 1690	410, 412, 414 (M^+, 6, 12, 6), 301, 303 (*d*, 40, 39), 167 ($M^+ - CBr_2CO_2Et$, 32), 152 (167-CH_3, 40), 137 (*b*-CBr_2CO_2Et, 39), 109 (*b*-$COCBr_2CO_2Et$, 100)
13	82	oil	$C_9H_{12}BrNO_2$ (246.1)	1720	248, 250 (M^+, 18, 17), 154 (*c*, 224), 139 (*d*, 100)[d], 121 (*d*-H_2O, 29), 69 ($C_5H_9^+$, 55)
14	73	60–62	$C_{10}H_{17}BrNO_2$ (263.2)	1725	262, 264 (M^+, 35, 35), 175, 178 ($M^+ - C_4H_8NO$, 95, 92)[d], 168 (*c*, 73)[d], 153 (*c*-CH_3, 90)[d], 111 ($C_7H_{11}O$, $C_8H_{15}^+$, 40, 40)[d]
trans-**18**	76	99–100	$C_{11}H_{17}N_2O_3$ (225.3)	2240, 1740	225 (M^+, 75), 210 (*d*, 18), 151 (*a*-CO_2CH_3, 35), 114 [$(CH_3)_2C{=}CHCO_2CH_3^+$, 100][d], 83 [$(CH_3)_2C^+CH{=}C{=}O$, 86][d]
19	82	115–117	$C_{10}H_{17}N_2O_2$ (197.3)	3420, 2240	197 (M^+, 62), 182 (*a*, 18), 151 (*a*-CH_2OH, 21), 110 ($C_8H_{14}^+$, 100)[d], 71 ($CH_3C{=}CHCH_2OH$, 71)[d]
trans-**20**	92	104–105	$C_{16}H_{22}NO_3$ (276.4)	1745, 1600	276 (M^+, 56), 132 [$(CH_3)_2C{=}CHPh^+$, 71], 117 (132-CH_3, 45), 56 ($C_3H_6N^+$, 100)[d]
trans-**21**	72	117–118	$C_{15}H_{22}NO_2$ (248.4)	3400	248 (M^+, 95), 145 [$(CH_3)_2C^+CH{=}CHPh$, 39], 132 [$(CH_3)_2C{=}CHPh^+$, 71], 56 ($C_3H_6N^+$, 100)[d]
22	85	101–102	$C_{10}H_{15}N_2O_2$ (195.2)	2240, 1730	195 (M^+, 75), 151 (*a*-CHO, 35)[d], 110 ($C_8H_{14}^+$, 100)[d], 82 ($C_5H_8^+$, 80)[d]
trans-**23**	78	108–109	$C_{15}H_{20}NO_2$ (246.3)	1720, 1600	246 (M^+, 72), 145 [$(CH_3)_2C^+CH{=}CHPh$, 46], 132 [$(CH_3)_2C{=}CHPh^+$, 91], 117 (132-CH_3, 70), 56 ($C_3H_6N^+$, 100)[d]
24	48	108–109	$C_{10}H_{13}N_2O_2$ (193.2)	2210, 1690	193 (M^+, 100), 163 (*b*, 44), 148 (*c*, 92), 120 (*c*-CO, 98)[d], 93 (C_7H_9, $C_6H_7N^+$, 42, 21)[d]
25	25	112–113	$C_{15}H_{18}NO_2$ (244.3)	1675, 1620	244 (M^+, 100), 229 (*a*, 44), 214 (*b*, 37), 199 (*e*, 33), 143 ($C_{10}H_{11}^+$, 58)[d]

[a] Satisfactory microanalyses obtained:

[b] Most frequently occuring types of ions are denoted as $a = (M - CH_3)^+$; $b = (M - NO)^+$; $c = (M - CH_3 - Br)^+$; $d = (M - NO - Br)^+$; $e = (M - CH_3 - NO)^+$.

[c] Mass spectra of nitroxides almost invariably contain this type of ion,[26] though usually less significant. As past experiences indicate, the origin of the $[M + H]^+$ species must at least partly be an reversible reaction of the nitroxides with moisture present in the air.

[d] Elemental composition(s) measured at R = 10000 by the peak matching technique.

***trans*-4-Cyano-3-hydroxymethyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy Radical (19):**

To a stirred solution of *trans*-**18** (2.25 g, 10 mmol) in dry *t*-BuOH (30 mL), $NaBH_4$ (378 mg, 10 mmol) is added and the mixture is refluxed. Dry MeOH (20 mL) is then added slowly during 1 h, and refluxing is continued for a further 2 h. The mixture is evaporated to dryness, the residue is taken up in brine (50 mL) to decompose the borohydride complexes, and is extracted with EtOAc (3 × 30 mL). The extract is dried ($MgSO_4$) and evaporated to dryness. The solid residue is crystallized from Et_2O/hexane to give pure *trans*-alcohol **19**.

Isomerization of *cis*/*trans* to *trans*-20:

A 30% solution of NaOMe (2.5 mL, 14 mmol) in dry MeOH is added to a solution of a mixture of *cis*/*trans*-**20** (3.32 g, 12 mmol) in dry MeOH (50 mL). The mixture is kept at 50 °C for 30 min, then diluted with brine (50 mL), acidified with 5% H_2SO_4, and extracted with Et_2O (2 × 30 mL). The extract is dried ($MgSO_4$) and evaporated. The residual semisolid is crystallized from Et_2O/hexane to give *trans*-**20**; yield: 3.05 g (92%); mp 104–105 °C.

^{1}H-NMR ($CDCl_3$/TMS) + PhNHNHPh additive: δ = 0.84, 1.20, 1.26, 2.0 (4 s, 3 H each, CH_3), 3.26 (d, 1 H, J = 12.0 Hz, H-3), 3.52 (d, 1 H, J = 12.0 Hz, H-4), 3.50 (s, 3 H, OCH_3).

***trans*-3-Hydroxymethyl-4-phenyl-2,2,5,5-tetramethylpyrrolidin-1-yloxy Radical (21):**

To a stirred solution of *cis*/*trans*-**20** (2.76 g, 10 mmol) in anhydrous toluene (20 mL), SMEAH (70% toluene solution, 5.6 mL, 20 mmol) is added dropwise, and the mixture is then refluxed for 3 h. The cooled mixture is poured into a stirred ice-cooled solution of 10% aq. NaOH (50 mL) and then extracted with Et_2O (3 × 30 mL). The organic phase is washed with 5% H_2SO_4 (30 mL), brine, dried ($MgSO_4$) and evaporated to dryness. For the oxidation of N–OH to N–O, the evaporated residue is taken up in $CHCl_3$ (30 mL) and aerated in the presence of PbO_2 (1 g) as catalyst for 30 min, filtered and flash chromatographed on silica gel ($CHCl_3/Et_2O$, 2:1) to give the *trans*-alcohol **21** (72%) as the major product; yield: 1.78 g (72%); mp 117–118 °C. The unsaturated aldehyde **25** (6%), and the saturated *trans* aldehyde **23** (10%) are obtained as minor products.

Oxidation of Nitroxyl *trans* Alcohols 19, 21 to Nitroxyl *trans* Aldehydes 22, 23 by Swern's Method; General Procedure:
To a cooled (−60 °C) and stirred solution of oxalyl chloride (1.39 g, 11 mmol) in dry CH_2Cl_2 (25 mL), DMSO (1.89 g, 24 mmol) in dry CH_2Cl_2 (5 mL) is added. After 15 min a solution of nitroxide *trans* alcohol **19** or **21** (10 mmol) in dry CH_2Cl_2 (20 mL) is added. After 15 min, Et_3N (5.05 g, 50 mmol) is added. The mixture is stirred at −60 °C for 30 min, allowed to warm to 0 °C and water (10 mL) is added dropwise. The organic phase is washed in turn with 5% H_2SO_4 (20 mL), 5% aq. $NaHCO_3$ (20 mL) and brine, dried ($MgSO_4$), and evaporated to dryness. The yellow residue is essentially pure enough for further reaction, but an analytical sample is obtained by preparative TLC on a silica gel plate (hexane/EtOAC, 2:1).

^{1}H-NMR ($CDCl_3$/TMS) + PhNHNHPh additive, *trans*-**22**: $\delta = 0.95$, 1.12, 1.22, 1.30 (3 s, 3 H each, CH_3), 2.7 (d, 1 H, J = 14.4 Hz, H-3), 2.86 (d, 1 H, J = 14.4 Hz, H-4), 9.45 (s, 1 H, CHO).

^{1}H-NMR ($CDCl_3$/TMS) + PhNHNHPh additive, *trans*-**23**: $\delta = 0.74$, 1.16, 1.20, 1.88 (4 s, 3 H each, CH_3), 3.01 (dd, 1 H, J = 12.0, 3.6 Hz, H-3), 3.38 (d, 1 H, J = 12.0 Hz, H-4).

Oxidation of *trans*-21 with Active MnO_2 and PbO_2:
To a well-stirred solution of *trans*-**21** (745 mg, 3 mmol) in CCl_4 (20 mL), MnO_2 (Merck, 3 g) and PbO_2 (1 g) are added, the mixture is refluxed for 6 h, and filtered. The filtrate is evaporated and flash chromatographed on silica gel. Three yellow bands are eluted with hexane/EtOAc (2:1) as eluent: first **25**; yield: 120 mg (16%), then *trans*-**23** yield: 37 mg (5%), and finally the unreacted *trans*-**21** (507 mg, 68%).

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