Synthesis of Simple Enantiopure Tetrahydro-β-carbolines and Tetrahydroisoquinolines

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Dedicated to Professor Yishen Zhang (Biology Department of Northeast Normal University, China) on the occasion of her 60th birthday

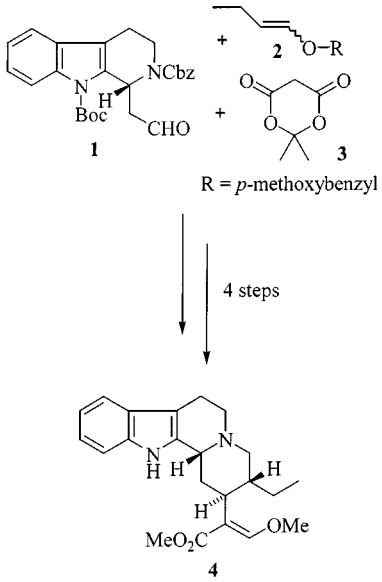
Keywords: Bischler−Napieralski reaction / Asymmetric synthesis / Hydrogenations / Oxidations / Tetrahydro-β-carbolines / Tetrahydroisoquinolines

Enantioselective hydrogenation of the imines **11**–**13**, **27** and **30** with the Ru complex (*R*,*R*)-**5** led to the tetrahydro-β-carbolines (1*S*)-**14**, (1*R*)-**21** and (1*S*)-**22**, and the tetrahydroisoquinoline (1*S*)-**31** with *ee* > 95%. By employing (*S*,*S*)-**5** the enantiomers are accessible. The imines **11**–**12** and **27** were obtained by oxidation of racemic **14**, **21** and **22** with $KMnO_4$ in > 58% yield.

Introduction

Tetrahydro-β-carbolines and tetrahydroisoquinolines are found abundantly in the plant kingdom and many of them exhibit important physiological activities.[1] This includes inhibition of monoamine oxidase, as well as in vivo filaricidal activity against *Litomosoides carinii* and *Acanthocheilonema viteae* in rodents.[2] On the other hand, C-1 substituted tetrahydro-β-carbolines and C-1-substituted tetrahydroisoquinolines are valuable substrates for the synthesis of indole and isoquinoline alkaloids.[3] Recently we have developed an efficient synthesis of the tetracyclic indole alkaloid hirsutine **(4)**, which is highly effective against the influenza A virus, using a domino-Knoevenagel hetero-Diels−Alder solvolysis−hydrogenation process (Scheme 1).[4,5] In this transformation, a mixture of the aldehyde **1**, Meldrum's acid **(3)** and 1-alkoxybutene **(2)** was heated to 60 °C and treated with methanol/K_2CO_3 followed by hydrogenation. The enantiopure aldehyde **1** was prepared by chromatographic separation of diastereomeric amides with camphanic acid. Since this method is not straightforward we were looking for a shorter way to prepare enantiopure **1** as well as other enantiopure C-1 substituted tetrahydro-β-carbolines and C-1 substituted tetrahydroisoquinolines which may be used in the described process.

Several methods for the synthesis of the described compounds using a stoichiometric amount of a chiral building block, auxiliary or reagent, as in the asymmetric Pictet−Spengler reaction,[6] the asymmetric nucleophilic and electrophilic introduction of a carbon unit at C-1,[7] as well as in the asymmetric reduction of dihydroisoquinolines



Scheme 1. Synthesis of hirsutine **4**

with chiral or achiral hydride reagents, have been described.[8] In addition, catalytic enantioselective procedures are known.[9] Especially useful seems to be the hydrogenation of cyclic imines using the chiral *N*-sulfonated diamine Ru complexes **5** as catalysts, as developed by Noyori et al.[10] Here, we describe the synthesis of enantiopure **14**, which is a precursor of the aldehyde **1**, and analogous tetrahydro-β-carbolines and tetrahydroisoquinolines starting from the corresponding imines using this process.

Results and Discussion

The catalyst **5** (Scheme 2) can be conveniently prepared in situ without isolation. A mixture of $[RuCl_2(\eta^6\text{-benzene})]_2$ and TsDPEN (Ru atom:TsDPEN = 1:1.2) in acetonitrile was stirred for 5 min and the brown suspension formed was

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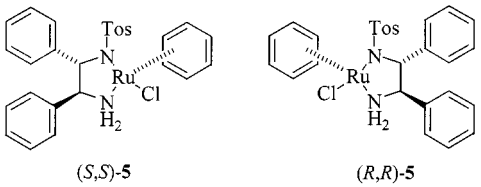
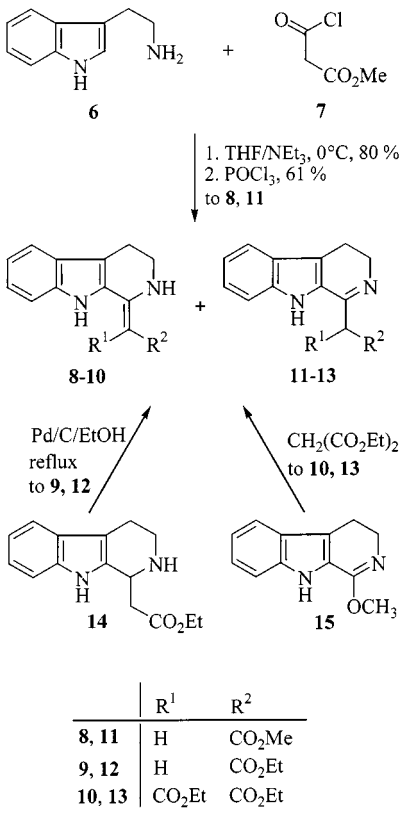


Scheme 2. Catalysts for the enantioselective hydrogenation

directly employed for the hydrogenation of the imines in a 5:2 formic acid/triethylamine mixture in acetonitrile.

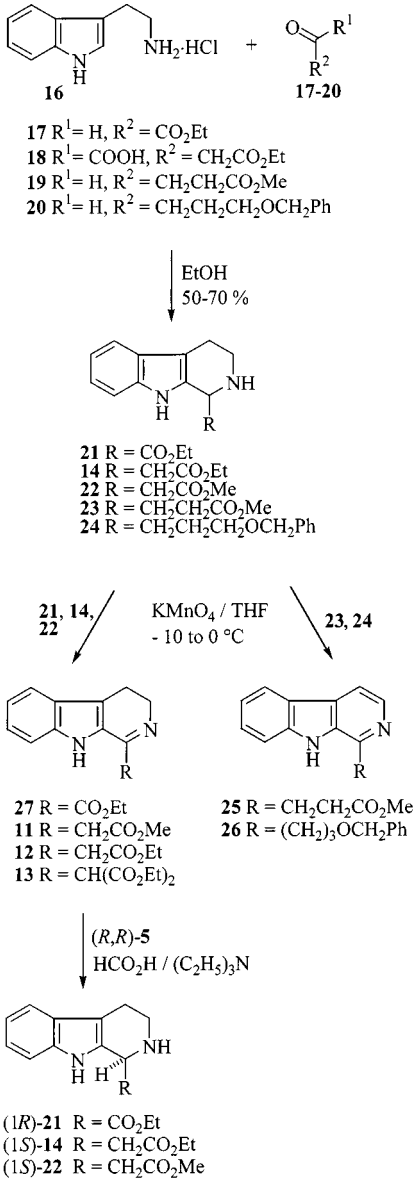
The necessary imines were prepared by applying the Bischler−Napieralski reaction and then the controlled oxidation and dehydrogenation of the appropriate 1,2,3,4-tetrahydro-β-carbolines.[11] The reaction of tryptamine **6** and the acid chloride **7** gave the enamine **8** and the imine **11** in a ratio of 9:1 in 50% yield,[12] whereas dehydrogenation of **14** with Pd/C (10%) in refluxing ethanol furnished a 10:1 mixture of **9** and **12**.[13] The reaction of **15** with diethyl malonate led to **10** and **13** in a ratio of 10:1 (Scheme 3).[14]

Looking for a more selective method for the synthesis of the necessary imines we prepared the corresponding racemic 1,2,3,4-tetrahydro-β-carbolines **14** and **21−24**, using a Pictet−Spengler reaction of tryptamine hydrochloride **(16)** and aldehydes or α-keto acids **17−20**, in good yield. The methyl ester **22** was obtained from the ethyl ester **14** by solvolysis with methanol/K_2CO_3. Oxidation of the tetrahydro-β-carbolines **14, 21** and **22** with solid potassium permanganate in tetrahydrofuran at −10 to 0 °C gave the corresponding imines in 58−97% yield,[11d] with the lowest



	R^1	R^2
8, 11	H	CO_2Me
9, 12	H	CO_2Et
10, 13	CO_2Et	CO_2Et

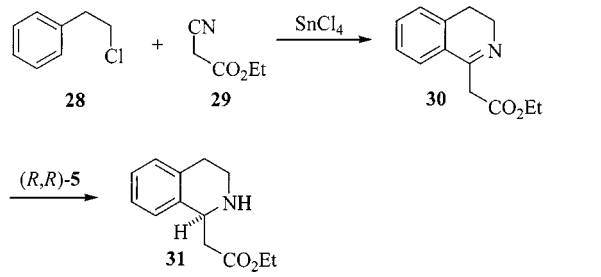
Scheme 3. Synthesis of β-carbolines



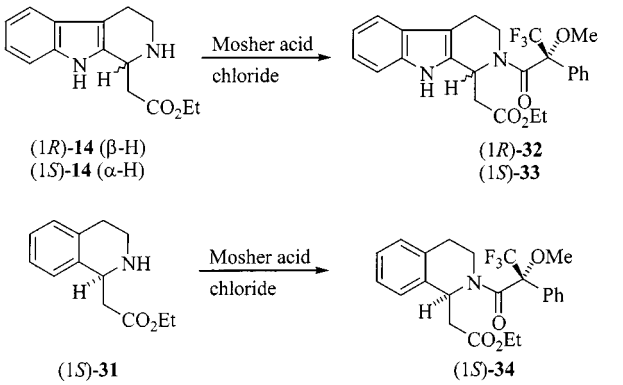
Scheme 4. Enantioselective synthesis of tetrahydro-β-carbolines

yield found for the methyl ester **22** due to its reduced stability relative to **14**. The oxidation of **23** and **24** did not lead to the desired imines but furnished the corresponding β-carbolines **25** and **26** instead.

For the hydrogenation, in some cases we used the mixture of the imines and enamines and in others the pure imines. Reaction of the mixtures **8/11**, **9/12** and **10/13** in formic acid/triethylamine 5:2 using the catalyst (*R*,*R*)-**5** gave (1*S*)-**14**, (1*R*)-**21** and (1*S*)-**22**, respectively, with 96−97% *ee* in 59−72% yield based on the amount of the imine in the mixture (Scheme 4). The enamines did not react under these conditions and were recovered unchanged. The hydrogenation of the imines **11−13** and **27** under the same conditions led to the C-1 substituted tetrahydro-β-carbolines (1*S*)-**14**, (1*R*)-**21** and (1*S*)-**22** in 50−93% yield based on racemic **14** and **21−22**, with 95−97% *ee*. The obtained products are almost pure, so in most cases chromatography is not



Scheme 5. Enantioselective synthesis of tetrahydroisoquinoline **31**



Scheme 6. Synthesis of Mosher derivatives

necessary. Since the catalyst (*S*,*S*)-**5** is also available, the enantiomeric tetrahydro-β-carbolines can also be prepared. Hydrogenation of **12** with (*S*,*S*)-**5** as catalyst led to (1*R*)-**14** in 93% yield and 97% *ee*.

For the synthesis of the enantiopure tetrahydroisoquinoline **31** the imine **30** was prepared by condensation of **28** with **29** in the presence of $SnCl_4$ to give **30** in 92% yield (Scheme 5).[15] Surprisingly, in this reaction only the imine is formed; the corresponding enamine was not found. Enantioselective hydrogenation of **30** with (*R*,*R*)-**5** gave (1*S*)-**31** in 85% yield and 99% *ee*.

The absolute configuration of the tetrahydro-β-carbolines (1*R*)-**14** and (1*S*)-**14** as well as tetrahydroisoquinoline **31** was determined according to an X-ray analysis of the corresponding Mosher acid derivative **32** (Scheme 6, Figure 1).[16]

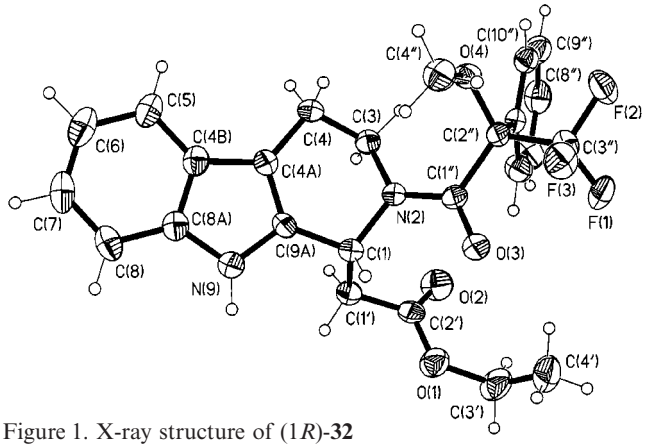


Figure 1. X-ray structure of (1*R*)-**32**

Conclusion

In summary, simple racemic C-1 substituted tetrahydro-β-carbolines were transformed into the enantiopure compounds using a sequence of oxidation with potassium permanganate and hydrogenation in formic acid/triethylamine with the Ru catalyst **5**. The products were obtained in 50−93% yield and 95−99% *ee*. Similarly, enantiopure C-1 substituted tetrahydroisoquinolines were prepared from the corresponding imine. Since both (*R*,*R*)-**5** and (*S*,*S*)-**5** are available, (1*S*)-tetrahydro-β-carbolines and (1*S*)-tetrahydroisoquinolines, as well as their enantiomers, can be prepared in excellent enantiopurity.

Experimental Section

General: All reactions were carried out under N_2 and monitored by TLC (POLYGRAM SIL G/UV$_{254}$, Macherey−Nagel GmbH & Co. KG). − All reagents from commercial suppliers were used without further purification. − Products were isolated by flash column chromatography on silica gel (Silica gel, particle size 0.040−0.063 mm, Macherey−Nagel GmbH & Co. KG). − HPLC: Kroma-system 2000; Detector DAD 440; Column: OR-D, Chiralcel; Solvents: MeOH/H_2O = 80/20; flow rate: 0.5 mL/min. − ^{1}H NMR and ^{13}C NMR: Varian XL-200 and VXR-200. − IR: Bruker VECTOR 22. − MS: Varian MAT 311A and Varian MAT 731 for high resolution.

Dichloro(η^6-benzene)ruthenium(II):[17] A mixture of $RuCl_3 \cdot H_2O$ (300 mg, 41% Ru), ethanol (4 mL) and cyclohexadiene (3 mL) was refluxed for 4 h, filtered, and dried under reduced pressure to give $[RuCl_2(C_6H_6)]_2$ (300 mg, 1.20 mmol, 98%) as a brown powder. − MS (DCI): *m*/*z* (%) = 285 $[M + 17 + 18]^+$. − $[RuCl_2(C_6H_6)]$ (250.1).

(1*R*,2*R*)-1,2-Diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine: A solution of *p*-TosCl (0.45 g, 2.40 mmol) in 5 mL THF was added to a mixture of (1*R*,2*R*)-(−)-1,2-diphenylethylenediamine (0.50 g, 2.40 mmol) in THF (20 mL) and triethylamine (1 mL) over a period of 0.5 h at 0 °C. After stirring for 12 h the solvent was removed under reduced pressure. The remaining solid was treated with aqueous sat. $NaHCO_3$ solution (40 mL) and CH_2Cl_2 (40 mL). The organic phase was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The crude product was purified by chromatography with ethyl acetate to give (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (0.79 g, 2.20 mmol, 90%) as a white solid. − $[\alpha]_D^{20} = -25.0$ (*c* = 0.2 in $CHCl_3$). − ^{1}H NMR (200 MHz, $CDCl_3$, D_2O exchange): δ = 7.25 (d, *J* = 8.0 Hz, 2 H, arom.), 7.55−7.00 (m, 10 H, Ph-H), 6.88 (d, *J* = 8.0 Hz, 2 H, arom.), 4.30 (d, *J* = 5.5 Hz, 1 H, C*H*−$NHSO_2$), 4.05 (d, *J* = 5.5 Hz, 1 H, C*H*−NH_2), 2.25 (s, 3 H, CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 142.4, 141.4, 139.3, 137.1, 129.1, 128.3, 128.2, 127.34, 127.26, 126.9, 126.8, 126.5 (arom.-C), 63.3, 60.4 (CH_2), 21.4 (CH_3). − MS (DCI): *m*/*z* (%) = 367 $[M + 1]^+$, 384 $[M + 18]^+$. − $C_{21}H_{22}O_2N_2S$ (366.5).

In a similar manner (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine was obtained.

General Procedure for Enantioselective Hydrogenation: Prior to use, the catalyst (*R*,*R*)-**5** or (*S*,*S*)-**5** was prepared by stirring 0.02 equiv. of dichloro(η^6-benzene)ruthenium(II) and 0.024 equiv. of (1*R*,2*R*)-

1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine or (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine in acetonitrile for 5 min. Formic acid/triethylamine (5:2, 2 mL/equiv.) and the obtained catalyst was added to a solution of 1 equiv. of the imine in acetonitrile (5 mL/equiv.). After stirring at room temp. for 8 h, the mixture was made basic by addition of aqueous Na_2CO_3 solution and extracted with ethyl acetate. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to afford the product.

1,2,3,4-Tetrahydro-β-carboline (1*R*)-21: Tryptamine hydrochloride (1.0 g, 5.1 mmol) was dissolved in ethanol (20 mL), cooled to 0° C, and then a solution of glyoxylic acid ethyl ester (1.3 mL, 6.1 mmol) in toluene was added. The reaction mixture was stirred over night at room temp., the solvents were removed under reduced pressure, and the obtained mixture was treated with sat. aqueous $NaHCO_3$ solution (30 mL) and ethyl acetate (30 mL). The aqueous phase was extracted with ethyl acetate (30 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography with ethyl acetate and triethylamine (100:1) afforded the compound **21** (0.62 g, 2.50 mmol, 50%) as a yellow oil which is not stable at room temp. −IR (film): $\tilde{\nu}$ = 3395, 2978, 2932, 1732, 743 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, indole-H), 7.60−7.05 (m, 4 H, arom.), 4.76 (br s, 1 H, 1-H), 4.30 (qd, *J* = 7.0, 1.2 Hz, 2 H, CH_2), 3.20−3.05 (m, 2 H, 3-H), 2.85−2.70 (m, 2 H, 4-H), 2.60 (s, 1 H, NH), 1.35 (t, *J* = 7.0 Hz, 3 H, CH_3). − HRMS ($C_{14}H_{16}N_2O_2$): calcd. 244.1221; found 244.1221.

To a vigorously stirred solution of **21** (0.20 g, 0.82 mmol) in dry tetrahydrofuran (20 mL) at −10 °C was added powdered potassium permanganate (1.0 g) in small portions over a period of 1 h while the temperature was raised to 0 °C. After stirring for 0.5 h TLC indicated that all of the starting material had been oxidized. The precipitate was filtered off and washed with THF (2 × 10 mL). The combined filtrates were concentrated to leave crude imine as a pale yellow foam (0.12 g, 0.50 mmol, 60%). According to the general procedure, the product (0.12 g, 0.50 mmol) was dissolved in acetonitrile (5 mL) and to the solution were added formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {$[RuCl_2(C_6H_6)]_2$, (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN}, and the mixture was stirred whilst warming from 0 °C to room temp. for 6 h. Purification of the crude product by flash chromatography with ethyl acetate/triethylamine (100:1) gave (1*R*)-**21** (80.0 mg, 0.33 mmol, 67%) as a brown oil. The spectra are identical with those of racemic **21**. − $[\alpha]_D^{20}$ = +15.2 (*c* = 0.2 in $CHCl_3$). The optical rotation is not highly accurate due to the instability of **21** at room temp.

1,2,3,4-Tetrahydro-β-carboline (1*S*)-14: To a vigorously stirred solution of **14**[18] (0.26 g, 1.00 mmol) in dry tetrahydrofuran (20 mL) at 0 °C was added powdered potassium permanganate (1.0 g) in small portions over 0.5 h, the reaction mixture was kept at 0° C and stirred for 1 h (TLC control). The precipitate was filtered off, washed with THF (2 × 10 mL), and the combined filtrates were evaporated to leave the crude imine as a pale yellow solid (0.25 g, 0.96 mmol, 97%). According to the general procedure, the crude product (0.19 g, 0.74 mmol) was dissolved in acetonitrile (5 mL) and to the solution were added formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {$[RuCl_2(C_6H_6)]_2$ (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN}. The mixture was stirred at room temp. for 8 h and afforded, after flash chromatography with ethyl acetate/EtOH/triethylamine (100:10:1), (1*S*)-**14** (0.18 g, 0.71 mmol, 96%) as a yellow oil. − $[\alpha]_D^{20}$ = +61.4 (*c* = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ = −44.0 (*c* = 0.5 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3314 (N−H Indol), 2982, 2848 (C−H), 1728 (C=O), 1180 (C−O−Et), 744 (Ph-H) cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.62 (br s, 1 H, N−H Indol), 7.52−7.02 (m, 4 H, arom.-H), 4.47 (t, *J* = 8.0, Hz, 1 H, 1-H), 4.42 (q, *J* = 8.0 Hz, 2 H, 3′-H), 3.01−3.03 (m, 2 H, 3-H), 2.81 (d, *J* = 8.0 Hz, 2 H, 1′-H), 2.73 (m, 2 H, 4-H), 1.85 (br s, 1 H, NH), 1.29 (t, *J* = 8.0 Hz, 3 H, 4′-H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.1 (C=O), 135.4, 134.9, 127.0, 121.6, 119.2, 118.0, 110.9, 108.9 (8 C, arom.), 61.0 (OCH_2), 48.7, 41.9 (C-1), 40.8 (C-3), 22.5 (C-4), 14.1 (CH_3). − MS (70 eV): *m*/*z* (%) = 258 (56) $[M]^+$, 171.0 (100) $[C_{11}H_{11}N_2]^+$. − HRMS ($C_{15}H_{18}N_2O_2$): calcd. 258.1368; found 258.1368.

14 (0.26 g, 1.0 mmol) was treated with catalyst (*S*,*S*)-**5** in the same manner to give (1*R*)-**14** (0.23 g, 0.90 mmol, 93%) as a yellow oil. − $[\alpha]_D^{20}$ = −61.9 (*c* = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ = +44.6 (*c* = 0.5 in MeOH).

1,2,3,4-Tetrahydro-β-carboline (1*S*)-22: A solution of ethyl ester **14** (0.50 g, 1.90 mmol) in MeOH (10 mL) was stirred with a catalytic amount of K_2CO_3 for 4 h to give the methyl ester (0.43 g, 1.80 mmol, 93%) as a yellow oil. As described for **14**, the product **22** (0.20 g, 82.0 μmol) was treated with $KMnO_4$ and (*R*,*R*)-**5** to give (1*S*)-**22** (0.11 g, 0.43 mmol, total yield 55%) as a yellow oil. − $[\alpha]_D^{20}$ = +50.0 (*c* = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ = −28.0 (*c* = 0.5 in MeOH). − IR (KBr): $\tilde{\nu}$ = 3394, 3110 (N−H), 1727 (C=O), 745 cm^{-1} (Ph-H). − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.60 (br s, 1 H, indole-NH), 7.60−7.00 (m, 4 H, arom.-H), 4.50 (t, *J* = 6.5 Hz, 1 H, 1-H), 3.80 (s, 3 H, OCH_3), 3.20−3.05 (m, 2 H, 3-H), 2.86 (d, *J* = 6.5 Hz, 2 H, 1′-H), 2.74 (t, *J* = 6.0 Hz, 2 H, 4-H), 1.85 (br s, 1 H, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.6 (C=O), 135.5, 134.8, 127.1, 121.8, 119.3, 118.1, 111.0, 109.0 (8 C, arom.-C), 52.1, 48.7 (OCH_3, C-1), 41.9, 40.6, 22.6 (3 CH_2). − HRMS ($C_{14}H_{16}N_2O_2$): calcd. 244.1211; found 244.1211.

1,2,3,4-Tetrahydro-β-carboline 23: A solution of 4-oxobutyric acid methyl ester (0.7 g, 6.0 mmol) and tryptamine hydrochloride (0.8 g, 4.0 mmol) in ethanol (50 mL) was stirred at room temp. for 20 h. After evaporating the solvent under reduced pressure, the residue was treated with CH_2Cl_2 (100 mL) and sat. aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic phases were dried with Na_2SO_4. The solvent was evaporated under reduced pressure to give **23** (0.95 g, 3.70 mmol, 70%) as a yellow oil after chromatography with ethyl acetate/triethylamine (100:1). − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H, indole-NH), 7.54−7.01 (m, 4 H, arom. H), 4.10−4.00 (m, 1 H, 1-H), 3.67 (s, 3 H, OCH_3), 3.35−3.19 (m, 1 H, 3-H), 3.13−2.93 (m, 1 H, 3-H), 2.71 (t, *J* = 5 Hz, 2 H, 4-H), 2.65−2.40 (m, 2 H, CH_2), 2.30−2.11 (m, 1 H, CH_2), 1.96 (dd, *J* = 7.0, 3.0 Hz, 1 H, CH_2), 0.78 (br s, 1 H, NH).

1,2,3,4-Tetrahydro-β-carboline 24: 4-Benzyloxybutyraldehyde[19] (1.8 g, 10 mmol) was added to a solution of tryptamine hydrochloride (1.9 g, 9.6 mmol) in ethanol (30 mL). After refluxing overnight ethanol was removed under reduced pressure. The products were treated with 2 N NaOH (30 mL) and ethyl acetate (30 mL), and the aqueous phase was washed with ethyl acetate (30 mL). The combined organic phases were washed with sat. aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. The solvent was removed and the remaining oil was purified by chromatography with EtOAc/EtOH/NEt_3 (100:10:1) to give the compound **24** as a yellow oil (2.1 g, 6.6 mmol, 70%). − ^1H NMR (200 MHz, $CDCl_3$): δ = 8.13 (s, 1 H, indole-H), 7.50−7.05 (m, 9 H, arom., Ph-H), 4.55 (s, 2 H, $PhCH_2$), 4.13 (s, 1 H, 1-H), 3.58 (t, *J* = 5.0 Hz, 2 H, CH_2), 3.40−3.20 (m,

1 H, 3-H_{eq}), 3.10−2.95 (m, 1 H, 3-H_{ax}), 2.66 (t, J = 5.0 Hz, 2 H, CH_2), 1.93−1.65 (m, 5 H, 2 CH_2, NH). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 138.1, 135.8, 135.6, 128.5, 127.85, 127.82, 127.4, 121.4, 119.2, 118.0, 110.8, 108.7 (arom.-C), 73.2 (OCH_2Ph), 70.4 (OCH_2), 52.2 (C-1), 42.2, 31.9, 26.0, 22.5 (4 CH_2). − HRMS ($C_{21}H_{24}N_2O$): calcd. 320.1888; found 320.1888.

1,2,3,4-Tetrahydroisoquinoline (1*S*)-31: A solution of ethyl cyanoacetate (11.3 g, 100 mmol), β-phenethyl chloride (16.0 g, 110 mmol) and anhydrous stannic chloride (26.1 g, 100 mmol) was heated for 3 h at 110 °C and then poured into 250 mL of 20% NaOH solution. The aqueous solution was kept below 5 °C by external cooling and addition of ice and then extracted with ether (3 × 200 mL). The combined organic phases were extracted with 10% HCl solution. The aqueous phase was cautiously neutralized with 35% NaOH solution and the resulting oil was taken up in ether. After drying and concentrating the ethereal solution, crude dihydroisoquinoline **30** (20.0 g, 92.0 mmol, 92%) remained as a pale yellow oil. − MS (DCI): *m*/*z* (%) = 218.1 [M^+ + 1]. − $C_{13}H_{15}NO_2$ (217.3).

According to the general procedure, compound **30** (200.0 mg, 0.920 mmol) was dissolved in acetonitrile (5 mL) and to the solution were added formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {[$RuCl_2(C_6H_6)$]$_2$, (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN} at 0 °C and the mixture was stirred whilst warming from 0 °C to room temp. for 8 h. After flash chromatography with ethyl acetate/EtOH/triethylamine (100:10:1) (1*S*)-**31 (**170.0 mg, 0.776 mmol, 85%) was obtained as a dark yellow oil. − $[\alpha]_D^{20}$ = −12.5 (*c* = 0.2 in $CHCl_3$); $[\alpha]_D^{20}$ = −10.0 (*c* = 0.2 in EtOH). − IR (KBr): $\tilde{\nu}$ = 3347 (NH), 1729 (C=O), 747 cm^{-1} (Ph-H). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.05 (m, 4 H, arom.-H), 4.46 (dd, J = 10.0, 4.0 Hz, 1 H, 1-H), 4.17 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.13−2.70 (m, 6 H, 3 CH_2), 2.50 (br s, 1 H, NH), 1.29 (t, J = 7.2 Hz, 3 H, CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 172.3 (C=O), 137.4, 135.4, 129.4, 128.3, 126.3, 125.9 (arom.-C) 60.6 (OCH_2), 52.7 (C-1), 41.3, 40.6, 29.7 (3 CH_2), 14.2 (CH_3). − HRMS ($C_{13}H_{17}NO_2$): calcd. 219.1259; found 219.1259.

1,2,3,4-Tetrahydro-β-carboline 14 and Enamine 10: α-Oxo-β-carboline[14a] (5.0 g, 27 mmol) was stirred with $POCl_3$ (20 mL) for 10 h at room temp. and then diethyl ether (50 mL) was added. The formed precipitate was isolated, dissolved in MeOH (100 mL), the solution stirred for 2 h at 60 °C and then cooled to room temp. Diethyl ether (150 mL) was then added and the newly formed precipitate was treated with sat. aqueous $NaHCO_3$ solution. The mixture was extracted with diethyl ether and the organic phase dried with Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography with ethyl acetate/pentane (1:2) to give compound **15**[14b] (2.5 g, 13 mmol, total yield 48%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.20 (s, 1 H, indole), 7.71−7.70 (m, 4 H, arom.-H), 3.95−3.80 (m, 5 H, OCH_3, 3-H), 2.90 (t, J = 8.0 Hz, 2 H, 4-H).

Compound **15** (200 mg, 1.00 mmol) was heated at 130 °C in malonic acid diethyl ester (5 mL) for 5 h and then the solvents were removed under reduced pressure. The crude products were not isolated, but, according to the general procedure, dissolved in acetonitrile (5 mL) and to the solution formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {[$RuCl_2(C_6H_6)$]$_2$ (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN} were added. The mixture was stirred at room temp. for 12 h and afforded enamine **10** (216.0 mg, 0.659 mmol, 66%) as a yellow solid and amine (3*S*)-**14** (18 mg, 70 μmol, 7%) as a yellow oil after flash chromatography with ethyl acetate/EtOH/triethylamine (100:10:1) (during chromatography saponification and decarboxylation to **14** occurred).

Enamine 10: − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.30, 9.85 (2 s, 2 H, NH, indole-H), 7.65−7.05 (m, 4 H, arom.-H), 4.30−4.05 (m, 4 H, OCH_2CH_3), 3.63−3.51 (m, 2 H, 3-H), 2.99 (t, J = 7.0 Hz, 2 H, 4-H), 1.33 (m, 6 H, CH_3). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 171.7, 169.9 (C=O), 151.9, (C-1), 136.9, 125.8, 125.1, 124.9, 120.2, 119.6, 118.5, 112.4 (arom. C), 88.5 [$C(CO_2Et)_2$], 61.4, 59.8 (OCH_2CH_3), 40.3 (C-3), 20.4 (C-4), 14.4, 14.1 (CH_3). − HRMS ($C_{18}H_{20}N_2O_4$): calcd. 328.1423; found 328.1423.

Amine (1*S*)-14: The spectra are identical with those shown above. − $[\alpha]_D^{20}$ = +62.5 (*c* = 0.2 in $CHCl_3$); $[\alpha]_D^{20}$ = −44.5 (*c* = 0.2 in MeOH).

1,2,3,4-Tetrahydro-β-carboline (1*S*)-22 and Enamine 8: To a stirred and cooled (0 °C) solution of tryptamine (2.00 g, 12.5 mmol) in CH_2Cl_2 (80 mL) and NEt_3 (20 mL) was added a solution of methyl malonyl chloride (1.90 g, 13.7 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at room temp. for 2 h, washed with saturated $NaHCO_3$ solution, and dried with Na_2SO_4. The solvent was removed and the crude product was purified by chromatography with ethyl acetate/pentane (2:1) to give the amide ester (2.7 g, 10 mmol, 83%) as a yellow solid. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.12 (s, 1 H, indole-NH), 7.70−6.95 (m, 6 H, arom. H, CONH), 3.75−3.55 (m, 5 H, OCH_3, CH_2), 3.28 (s, 2 H, CH_2), 2.98 (t, J = 7.0 Hz, 2 H, 4-H).

The amide ester (200.0 mg, 0.769 mmol) was stirred in $POCl_3$ (5 mL) at room temp. for 12 h. Excess $POCl_3$ was evaporated in vacuo and the residue was basified with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Usual workup gave the crude product which was, according to the general procedure, treated with formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {[$RuCl_2(C_6H_6)$]$_2$ (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN}. The mixture was stirred at room temp. for 8 h and afforded enamine **8** (110 mg, 0.45 mmol, 55%) and amine (1*S*)-**22** (12 mg, 49 μmol, 5.9%) as yellow oils after flash chromatography with ethyl acetate/EtOH/triethylamine (100:10:1).

Enamine 8: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.13 (s, 2 H, NH, indole-H), 7.62−7.05 (m, 4 H, arom.-H), 4.85 (s, 1 H, CH=C), 3.74 (s, 3 H, OCH_3), 3.55 (t, J = 6.0 Hz, 2 H, CH_2), 2.97 (t, J = 6.0 Hz, 2 H, CH_2).

Amine (1*S*)-22: the spectra are identical with those shown above. − $[\alpha]_D^{20}$ = +51.2 (*c* = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ = −29.0 (*c* = 0.5 in MeOH).

1,2,3,4-Tetrahydro-β-carboline (1*S*)-14 and Enamine 9: Tetrahydro-β-carboline **14** (258 mg, 1.00 mmol) was refluxed in EtOH (10 mL) with Pd/C (10%, 100 mg) for 4 h. The catalyst was removed by filtration and the solvent was evaporated. According to the general procedure, the obtained crude product was treated with formic acid/triethylamine (2 mL) and the preformed catalyst (*R*,*R*)-**5** {[$RuCl_2(C_6H_6)$]$_2$ (6.0 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-tolylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 2.0 mL CH_3CN} and stirred at room temp. for 8 h. Purification by flash chromatography with ethyl acetate/EtOH/triethylamine (100:10:1) gave enamine **9** (174.0 mg, 0.680 mmol, 68%) and amine (1*S*)-**14** (17 mg, 66 μmol, 6.5%) as yellow oils.

Enamine 9: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.45−8.25 (br s, 2 H, NH, indole-H), 7.57−7.14 (m, 4 H, arom. H), 4.90 (s, 1 H,

CH=C), 4.17 (q, J = 7.2 Hz, 2 H, OCH_2), 3.60 (dt, J = 6.9, 2.5 Hz, 2 H, NCH_2), 2.99 (t, J = 7.0 Hz, 2 H, CH_2), 1.30 (t, J = 7.2 Hz, 3 H, CH_3).

Amine (1*S*)-14: the spectra are identical with those shown above. − $[\alpha]_D^{20}$ = +61.2 (c = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ = −44.3 (c = 0.5 in MeOH).

Determination of Configuration and *ee* Value From Mosher Acid Derivatives: To a solution of (1*R*)-**14** (20 mg, 78 μmol) in CH_2Cl_2 (5 mL) and triethylamine (0.5 mL) at 0 °C, was added a solution of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (20.0 mg, 0.96 mmol) in THF (2 mL). After stirring at room temp. for 8 h, the reaction mixture was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated under reduced pressure to give compound **32** as a white solid (32 mg, 68 μmol, 85%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.95 (s, 1 H, indole-NH), 7.72−6.90 (m, 9 H, Ar-H), 6.00 (dd, J = 11.0, 2.0 Hz, 1 H, 1-H), 5.19, 4.88 (dd, d, J = 11.0, 2.0 Hz, J = 8.0 Hz, 0.2 H, 3-H_{eq}), 4.22−4.03 (m, 2.8 H, 3-H_{eq}, OCH_2), 3.78, 3.70 (2 s, 3 H, OCH_3), 3.25−2.50 (m, 5 H, 3-H_{ax}, 4-H, 1′-H), 1.30 (t, J = 8.0 Hz, 3 H, CH_3). − HRMS ($C_{25}H_{25}F_3N_2O_4$): calcd. 474.1766; found 474.1766.

To a solution of (1*S*)-**14** (20 mg, 78 μmol) in CH_2Cl_2 (5 mL) and triethylamine (0.5 mL) at 0 °C, was added a solution of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (20.0 mg, 0.96 mmol) in THF (2 mL). After stirring at room temp. for 8 h, the reaction mixture was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated under reduced pressure to give compound **33** as a white solid (34 mg, 72 μmol, 90%). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.91, 8.65 (2 s, 1 H, indole-NH), 7.75−6.95 (m, 9 H, Ar-H), 6.15−5.81 (m, 1 H, 1-H), 4.95−5.10 (m, 0.2 H, 3-H_{eq}), 4.5−3.9 (m, 2.8 H, 3-H_{eq}, OCH_2), 3.80, 3.45 (2 s, 3 H, OCH_3), 3.13−2.05 (m, 5 H, 3-H_{ax}, 4-H, 1′-H), 1.30 (t, J = 8.0 Hz, 3 H, CH_3). − HRMS ($C_{25}H_{25}F_3N_2O_4$): calcd. 474.1766; found 474.1766.

To a solution of (1*S*)-**31** (20 mg, 92 μmol) in CH_2Cl_2 (5 mL) and triethylamine (0.5 mL) at 0 °C, was added (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride. After stirring at room temp. for 8 h, the reaction mixture was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated under reduced pressure to give compound **34** as a yellow oil. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 −7.05 (m, 9 H, arom. H), 6.12, 6.00 (2 t, J = 5.5 Hz, 1 H, 1-H), 4.25−3.25 (m, 6 H, CO_2CH_2, OCH_3, 3-H_{eq}), 2.95−2.05 (m, 5 H, CH_2, 3-H_{ax}), 1.30−1.20 (m, 2 H, CH_3). − HRMS ($C_{24}H_{26}F_3NO_4$): calcd. 449.1814; found 449.1814.

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[1] B. T. Ho, W. M. McIsaac, K. E. Walker, V. Estevez, *Journal of Pharmaceutical Sciences* **1968**, *57*, 269−273.
[2] A. Agarwal, S. K. Agarwal, S. N. Singh, N. Fatma, R. K. Chatterjee, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 225−228.
[3] [3a] Z. Czarnocki, D. B. MacLean, W. A. Szarek, *Can. J. Chem.* **1986**, *64*, 2205−2210. − [3b] Z. Czarnocki, D. B. MacLean, W. A. Szarek, *Bull. Soc. Chim. Belg.* **1986**, *95*, 749−770.
[4] [4a] Review: L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136. − [4b] L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137−170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131−163. − [4c] L. F. Tietze, J. Bachmann, J. Wichmann, O. Burkhard, *Synthesis* **1994**, 1185−1194. − [4d] L. F. Tietze, J. Bachmann, J. Wichmann, Y. Zhou, T. Raschke, *Liebigs Ann./Recueil* **1997**, 881−886.
[5] L. F. Tietze, Y. Zhou, *Angew. Chem.* **1999**, *111*, 2076−2077; *Angew. Chem. Int. Ed.* **1999**, *38*, 2045−2047.
[6] [6a] D. L. Comins, M. Badawi, *Tetrahedron Lett.* **1991**, *32*, 2995−2996. − [6b] T. Kawate, H. Yamada, M. Matsumizu, A. Nishida, M. Nakagawa, *Synlett.* **1997**, 761−762. − [6c] E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797−1842. − [6d] H. Waldmann, G. Schmidt, M. Jansen, J. Geb, *Tetrahedron* **1994**, *50*, 11865−11884.
[7] A. I. Meyers, *Tetrahedron* **1992**, *48*, 2589−2612.
[8] [8a] K. Yamada, M. Takeda, T. Iwakuma, *J. Chem. Soc. Perkin Trans. 1* **1983**, 265−270. − [8b] R. P. Polniaszek, C. R. Kaufman, *J. Am. Chem. Soc.* **1989**, *111*, 4859−4863.
[9] [9a] H. B. Kagan, N. Langlois, T. P. Dang, *J. Organomet. Chem.* **1975**, *90*, 353−365. − [9b] K. Achiwa, *Heterocycles* **1977**, *8*, 247−248. − [9c] C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952−8965. − [9d] C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 11703−11714. − [9e] M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, R. Noyori, *J. Org. Chem.* **1994**, *59*, 297−310. − [9f] T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 2661−2664. − [9g] T. Morimoto, N. Suzuki, K. Achiwa, *Heterocycles* **1996**, *43*, 2557−2560. − [9h] T. Morimoto, N. Suzuki, K. Achiwa, *Tetrahedron: Asymmetry* **1998**, *9,* 183−187. − [9i] J. Kang, J. B. Kim, K. H. Cho, B. T. Cho, *Tetrahedron: Asymmetry* **1997**, *8*, 657−660.
[10] [10a] N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. − [10b] R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97−102.
[11] [11a] W. H. Perkin, R. Robinson, *J. Chem. Soc.,* **1919**, *115*, 933−967. − [11b] R. H. F. Manske, W. H. Perkin, R. Robinson, *J. Chem. Soc.* **1927**, 1−14. − [11c] J. D. Spenser, *Can. J. Chem.* **1959**, *37*, 1851−1858. − [11d] S. Misztal, M. Cegla, *Synthesis* **1985**, 1134−1135.
[12] Y. Torisawa, A. Hashimoto, M. Nakagawa, H. Seki, R. Hara, T. Hino, *Tetrahedron* **1991**, *47*, 8067−8078.
[13] S. Murahashi, N. Yoshimura, T. Tsumiyama, T. Kojima, *J. Am. Chem. Soc.* **1983**, *105*, 5002−5011.
[14] [14a] F. Bracher, D. Hildebrand, *Liebigs Ann. Chem.* **1992**, 1315−1319. − [14b] H. Henecka, H. Timmler, R. Lorenz, *Med. Chem. (Leverkusen Ger.)* **1963**, *7*, 277−286.
[15] W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, A. I. Meyers, *J. Org. Chem.* **1965**, *30*, 3667−3671.
[16] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-140352. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44(1223)336−033; E-mail: deposit@ccdc.cam.ac.uk].
[17] [17a] M. A. Bennett., A. K. Smith, *J. Chem. Soc. Dalton Trans.* **1974**, 233−241. − [17b] G. Winkhaus, H. Singer, *J. Organomet. Chem.* **1967**, *7*, 487−491.
[18] G. B. Kline, *J. Am. Chem. Soc.* **1959**, *81*, 2251−2255.
[19] M. I. Dawson, M. Vasser, *J. Org. Chem.* **1977**, *42*, 2783−2785.

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