Electronic Supporting Information

Efficient Resolution of Racemic N-Benzyl β³-Amino Acids by Iterative Liquid-Liquid Extraction with a Chiral (Salen)Cobalt(III) Complex as Enantioselective Selector

Pawel Dzygiel, a Chiara Monti, a Umberto Piarulli*b and Cesare Gennari*a

a Dipartimento di Chimica Organica e Industriale, Centro di Eccellenza C.I.S.I., Università degli Studi di Milano, Via G. Venezian, 21, 20133 Milano, Italy
b Dipartimento di Scienze Chimiche e Ambientali, Università degli Studi dell’Insubria, Via Valleggio, 11, 22100 Como, Italy

(rac)-3-Benzylamino-3-phenylpropionic acid (N-benzyl-β³-Homophenylglycine - N-Bn-β³-hPhg).

N-Bn-β³-hPhg (HPLC trace of a racemic solution of N-Bn-β³-hPhg)
$N$-Bn-$\beta^3$-hPhg (\textsuperscript{1}H-NMR, D\textsubscript{2}O-NaOH)

$N$-Bn-$\beta^3$-hPhg (\textsuperscript{13}C-NMR, D\textsubscript{2}O-NaOH)
(rac)-3-Benzylaminobutyric acid (N-benzyl-β<sup>3</sup>-homoalanine - N-Bn-β<sup>3</sup>-hAla).

\[ \text{N-Bn-β}^3\text{-hAla (HPLC trace of a racemic solution of N-Bn-β}^3\text{-hAla)} \]
N-Bn-β³-hAla ($^1$H-NMR, D$_2$O)

N-Bn-β³-hAla ($^{13}$C-NMR, D$_2$O)
(rac)-3-Benzylamino-4-methyl pentanoic acid (N-benzyl-β3-Homovaline - N-Bn-β3-hVal).

\[
\text{COOEt} \xrightarrow{1) \text{BnNH}_2, \text{Benzene, reflux}} \xrightarrow{2) \text{NaBH}_3\text{CN/AcOH}} \text{COOEt} \xrightarrow{1) \text{KOH/MeOH}} \xrightarrow{2) \text{HCl/MeOH}} \text{COOH}
\]

\(N\text{-Bn-β}^3\text{-hVal}\) (HPLC trace of a racemic solution of \(N\text{-Bn-β}^3\text{-hVal}\)
N-Bn-β3-hVal (1H-NMR, D2O)

N-Bn-β3-hVal (13C-NMR, D2O)
Extraction/separation Scheme

Co^{III}(R,R-1)OAc → Org3

1) L-Ascorbic Acid
2) Dowex 50X-X8

Co^{III}(S,S-1)OAc

Org1

Co^{III}(R,R-1)OAc

R = Ph N-Bn-β^3-hPhg
R = Me N-Bn-β^3-hAla
R = i-Pr N-Bn-β^3-hVal

Co^{III}(R,R-1)OAc

Org2

Co^{III}(S,S-1)OAc

Org2'

Org3'

Org4'

Org5'

Org6'

H_2O

CH_2Cl_2

t-Bu

t-Bu

t-Bu

t-Bu

Co^{III}(R,R-1)OAc

1 equiv

OAc

Co^{III}(R,R-1)OAc

2 equiv

R = Ph N-Bn-β^3-hPhg
R = Me N-Bn-β^3-hAla
R = i-Pr N-Bn-β^3-hVal
Extraction of $N$-Bn-$\beta^3$-hPhg.

$^1$H-NMR spectrum in CDCl$_3$ of (R,R)-[Co$^{III}$(1)(N-Bn-$\beta^3$-hPhg)] obtained from Org1

$^{13}$C-NMR spectrum in CDCl$_3$ of (R,R)-[Co$^{III}$(1)(N-Bn-$\beta^3$-hPhg)] obtained from Org1
HPLC trace of the $N$-Bn-$\beta^3$-hPhg solution (Aq4) obtained after the second extraction of $N$-Bn-$\beta^3$-hPhg with ($S,S$)-[Co$^{III}$($\mathbf{1}$)(OAc)] and cleavage with ascorbic acid ($t_r = 8.5$ min, $S$ enantiomer; $t_r = 9.4$ min, $R$ enantiomer; 90% ee).

HPLC trace of the solution of $N$-Bn-$\beta^3$-hPhg (Aq6) obtained from the organic phase (Org3) following the second extraction of $N$-Bn-$\beta^3$-hPhg with ($R,R$)-[Co$^{III}$($\mathbf{1}$)(OAc)] and cleavage with ascorbic acid ($t_r = 8.6$ min, $R$ enantiomer; $t_r = 9.4$ min, $S$ enantiomer; 90% ee).
$^1$H-NMR spectra in CDCl$_3$ of (R,R)-[Co$^{III}$](I)(N-Bn-$\beta^3$-hPhg)] obtained from Org2'.

$^{13}$C-NMR spectra in CDCl$_3$ of (R,R)-[Co$^{III}$](I)(N-Bn-$\beta^3$-hPhg)] obtained from Org2'.
HPLC trace of the aqueous phase (Aq3’) following the second extraction of N-Bn-β-hPhg with (R,R)-[Co\textsuperscript{III}(1)(OAc)] (t\textsubscript{S} = 8.1 min, S enantiomer; t\textsubscript{R} = 9.1 min, R enantiomer; 93% ee).

\[1^H\text{-NMR spectra in CDCl}_3\text{ of (S,S)}-[Co\textsuperscript{III}(1)(N-Bn-β-hPhg)] \text{ obtained from Org3’}.\]
\(^{13}\text{C}-\text{NMR} \) spectra in CDCl\(_3\) of (S,S)-[Co\text{III}(1)(N-Bn-\beta^3-hPhg)] obtained from Org3’.

HPLC trace of the aqueous phase (Aq5’) following the second extraction of N-Bn-\beta^3-hPhg with (S,S)-[Co\text{III}(1)(OAc)] (t\(_r\) = 8.5 min, S enantiomer; t\(_r\) = 9.7 min, R enantiomer; 93% ee).
Extraction of \( N\text{-Bn-}\beta^3\text{-hAla}. \)

HPLC trace of the \( N\text{-Bn-}\beta^3\text{-hAla} \) solution (Aq4) following the second extraction of \( N\text{-Bn-}\beta^3\text{-hAla} \) with \((S,S)\text{-}[Co^{III}(I)(OAc)] \) \( (t_e = 37.0 \text{ min}, R \text{ enantiomer}; t_e = 40.5 \text{ min}, S \text{ enantiomer}; 88\% \text{ ee}). \)

HPLC trace of the solution of \( N\text{-Bn-}\beta^3\text{-hAla} \) (Aq6) following the second extraction of \( N\text{-Bn-}\beta^3\text{-hAla} \) with \((R,R)\text{-}[Co^{III}(I)(OAc)] \) \( (t_e = 35.1 \text{ min}, R \text{ enantiomer}; t_e = 40.8 \text{ min}, S \text{ enantiomer}; 90\% \text{ ee}). \)
HPLC trace of the aqueous phase (Aq3’) following the second extraction of N-Bn-β^3-hAla with (R,R)-[Co^{III}(I)(OAc)] (t_r = 33.5 min, R enantiomer; t_r = 37.1 min, S enantiomer; 36% ee).

HPLC trace of the aqueous phase (Aq5’) following the second extraction of N-Bn-β^3-hAla with (S,S)-[Co^{III}(I)(OAc)] (t_r = 33.2 min, R enantiomer; t_r = 38.1 min, S enantiomer; 83% ee).
Extraction of $N$-Bn-$\beta^3$-hVal.

HPLC trace of the $N$-Bn-$\beta^3$-hVal solution (Aq4) following the second extraction of $N$-Bn-$\beta^3$-hVal with $(S,S)$-[Co$^{III}$(I)(OAc)] [$t_r = 7.5$ min, (+) enantiomer; $t_r = 9.3$ min, (-) enantiomer; 90% ee]

HPLC trace of the solution of $N$-Bn-$\beta^3$-hVal (Aq6) following the second extraction of $N$-Bn-$\beta^3$-hVal with $(R,R)$-[Co$^{III}$(I)(OAc)] [$t_r = 7.7$ min, (+) enantiomer; $t_r = 9.0$ min, (-) enantiomer; 93% ee].
HPLC trace of the $N$-Bn-$\beta^3$-hVal solution (Aq3') following the second extraction of $N$-Bn-$\beta^3$-hVal with $(R,R)$-[$Co^{III}(1)(OAc)]$ [$t_r = 7.8 \text{ min}, (\text{+}) \text{ enantiomer}; t_r = 9.8 \text{ min}, (\text{-}) \text{ enantiomer; } 80\% \text{ ee}$]

![HPLC trace of the $N$-Bn-$\beta^3$-hVal solution (Aq3').](image)

HPLC trace of the solution of $N$-Bn-$\beta^3$-hVal (Aq5') following the second extraction of $N$-Bn-$\beta^3$-hVal with $(S,S)$-[$Co^{III}(1)(OAc)]$ [$t_r = 7.3 \text{ min}, (\text{+}) \text{ enantiomer; } t_r = 8.4 \text{ min}, (\text{-}) \text{ enantiomer; } 92\% \text{ ee}$].

![HPLC trace of the solution of $N$-Bn-$\beta^3$-hVal (Aq5').](image)

Attribution of the absolute configuration to $N$-Bn-$\beta^3$-hVal: by analogy with the complexation selectivity shown for $N$-Bn-$\beta^3$-hPhg and $N$-Bn-$\beta^3$-hAla, we attribute to (R)-$N$-Bn-$\beta^3$-hVal the (R) absolute configuration: $[\alpha]_D^{24} = +35.6, c 0.80 \text{ in MeOH, } 100\% \text{ ee in favour of (R)-enantiomer.}$