Asymmetric Synthesis ofb-Haloarylb-Amino Acid Derivatives

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Lithium*N*-benzyl-*N*-a-methyl-4-methoxybenzylamide may be employed as a homochiral ammonia equivalent for the synthesis of homochiralb-haloaryl-b-amino acid derivatives*via*a strategy involving its conjugate addition toa,b-unsaturatedb-haloaryl acceptors and subsequent oxidative deprotection with ceric ammonium nitrate.

Introduction

b-haloaryl-b-amino acids are an important sub-class ofb-amino acids which have been widely employed within medicinal chemistry. {1} Previous synthetic strategies employed for the synthesis of these pharmacologically active compounds include the enzymatic resolution ofb-haloarylb-amino esters using the lipase Amano PS, {2} diastereoselective cycloaddition betweenb-haloaryl imines and ketenes, {3} andthe Lewis acid catalyzed addition of a tributylstannane to a chiral oxazolidine. {4} While these reports represent efficient approaches towards the asymmetric synthesis of specificb-haloarylb-amino acid targets, they lack generality and are therefore not applicable to the synthesis of libraries of homochiralb-haloarylb-amino acid derivatives. {5} We have previously shown that a wide range ofb-amino acid derivatives can be efficiently prepared*via*the conjugate addition of homochiral lithium amides derived froma-methylbenzylamine toa,b-unsaturated esters and subsequent reductive*N*-deprotection. {6} While these approaches offer versatile routes tob-amino acid derivatives,b-haloarylb-amino acid derivatives are incompatible with this methodology as the haloaryl functionality within the substrate is labile under either the hydrogenolytic or Birch reduction conditions required for deprotection of the*N*-a-methylbenzyl group. We have previously described the development of a third generation homochiral ammonia equivalent, lithium (*S*)-*N*-benzyl-*N*-a-methyl-4-methoxybenzylamide, for the asymmetric synthesis of homochiralb-amino acids andb-lactams which involves deprotection via oxidative debenzylation {7} and now describe herein how this methodology may be employed for the asymmetric synthesis of a wide range of homochiralb-haloaryl-b-amino acid derivatives. Part of this work has been previously communicated. {8}

Results

Synthesis of*tert*-butylb-haloaryla,b-unsaturated esters

Our synthetic strategy for the synthesis ofb-haloarylb-amino esters relied upon the conjugate addition of homochiral lithium*N*-benzyl-*N*-a-methyl-4-methoxybenzylamide**1**to suitably functionalisedb-haloaryla,b-unsaturated esters (Figure 1).

Figure 1: General Strategy for the Asymmetric Synthesis ofb-haloaryl-b-amino acid derivatives

The required fluoro-, chloro-, bromo- and iodo- substituted (*E*)-*tert*-butylb-haloarylprop-2-enoate conjugate acceptors**2**-**9**were readily prepared in >95% crude d.e. {9} *via*Wadsworth-Emmons reaction of the parent benzaldehyde with the lithium anion of*tert*-butyl diethylphosphonoacetate. Purification gave multigram quantities of**2**-**9**in high yields as single diastereoisomers (Scheme 1).

Scheme 1 *Reagents and Conditions:*(i)*tert*-butyl diethylphosphonoacetate

-BuLi (1.10 eq), THF, -78CHAR:730C then haloaryl aldehyde, -78CHAR:730C to RT.

Conjugate addition ofN-benzyl-N-a-methyl-4-methoxybenzylamide1toa,b-unsaturated esters 2-9

Conjugate addition of (*S*)-**1**to the fluoro- and iodo- substituteda,b-unsaturated esters**2-5**and (*R*)-**1**to the bromo- and chloro- substituteda,b-unsaturated esters**6-9**afforded the*N*-benzyl-*N*-a-methyl-4-methoxybenzyl protectedb-amino esters**10-17**with high levels of crude diastereoselectivity (88-94% d.e.). While 3-fluoro (3*R*,a*S*)-**10**, 2-iodo (3*R*,a*S*)-**11**and 2-bromo (3*S*,a*R*)-**15**could be purified by fractional recrystallisation (Et [2] O:hexane) to 97% d.e., 98% d.e. and 98% d.e. respectively, repeated chromatography of the oilyb-amino esters**12-14**and**16-17**did not enhance the diastereoselectivity of the products arising from the crude reaction mixtures.b-amino esters**12-14**and**16-17**were therefore carried forward as mixtures of diastereoisomers (Scheme 2).

Scheme 2 *Reagents and Conditions:*(i) (*S*)-**1**(1.6eq), THF, -78CHAR:730C; (ii) (*R*)-**1**(1.6eq), THF, -78CHAR:730C.

{#} as shown by {1} H NMR spectroscopic analysis.

The absolute configurations of**10**-**17**were assigned by analogy to the model previously developed to explain the stereoselectivity observed during addition of homochiral lithium amides toa,b-unsaturated acceptors, {10} and the known stereoselectivity of lithium amide**1**upon addition to*tert*-butyl cinnamate. {7} 3-Fluoro (3*R*,a*S*)-**10**(97% d.e.), 2-iodo (3*R*,a*S*)-**11**(98% d.e.), and 2-bromo (3*S*,a*R*)-**15**(98% d.e.), were subjected to mono*N*-benzylic deprotection*via*treatment with CAN (2.1eq), furnishing the*N*-a-methyl-4-methoxybenzyl protectedb-amino esters**18-20**in 75-86% yield. Further treatment of 3-fluoro (3*R*,a*S*)-**18**, 2-iodo (3*R*,a*S*)-**19**and 2-bromo (3*S*,a*R*)-**20**with CAN (4.0eq) gave the desired*tert*-butyl 3-amino-b-haloarylpropanoates**21-23**in 51-68% yield. The e.e. of eachb-amino ester**21-23**was shown to be 97-98%,*via*derivatisation with MosherCHAR:8217s acid chloride and comparison of the {19} F and {1} H NMR spectra of the resulting amides with authentic racemic samples (Scheme 3).

Scheme 3 *Reagents and conditions:*(i) CAN (2.1eq), MeCN:H [2] O (5:1), RT; (ii) CAN (4.0eq), MeCN:H [2] O (5:1), RT.

Treatment of tertiaryb-amino ester**12**(88% d.e.) with CAN (2.1eq) gave (3*R*,a*S*)-*tert*-butyl 3-(*N*-a-methyl-4-methoxybenzylamino)-3-(iodophenyl)propanoate**24**in 77% yield and 88% d.e. (3*R*,a*S*)-**24**could not be purified to homogeneity at this stage by chromatography, so further treatment of (3*R*,a*S*)-**24**(88% d.e.) with CAN (4.0eq) gave (*R*)-*tert*-butyl 3-amino-3-iodophenylpropanoate**25**in 49% yield and in 88% e.e. as determined by MosherCHAR:8217s ester analysis (Scheme 4).

Scheme 4 *Reagents and Conditions:*(i) CAN (2.1eq), MeCN:H [2] O (5:1), RT; (ii) CAN (4.0eq), MeCN:H [2] O (5:1), RT.

An alternative deprotection strategy was next devised to enable the corresponding (*R*)-methyl ester**27**to be obtained in high enantiomeric excess. Thus, treatment of (3*R*,a*S*)-**24**(88% d.e.) with methanolic HCl afforded the methyl ester hydrochloride salt of (3*R*,a*S*)-**26**which was recrystallised {ethyl acetate:hexane (6:1)}. Conversion of (3*R*,a*S*)-**26**.HCl to its free amine using saturated aqueous NaHCO [3] solution gave (3*R*,a*S*)-**26**in 75% overall yield and 97% d.e. as shown by {1} H NMR spectroscopic analysis. Deprotection of**26** *via*treatment with CAN afforded (*S*)-**27**in 48% yield. The e.e. of (*S*)-**27**was shown to be 97% by MosherCHAR:8217s amide derivatisation and comparison of the {19} F NMR spectrum with an authentic racemic standard

(Scheme 5).

Scheme 5 *Reagents and Conditions:*(i) HCl, MeOH; (ii) recrystallisation {ethyl acetate:hexane (6:1)}; (iii) NaHCO [3(aq)] ; (iv) CAN (4.0eq), MeCN:H [2] O (5:1).

This protocol was therefore adopted for the deprotection of thoseb-amino esters**13-14**,**16-17**which could not be purified to homogeneity after the conjugate addition of lithium amide**1**to the appropriatea,b-unsaturated acceptor. Thus, CAN mono-debenzylation of**13-14**,**16-17**gave mono-deprotected secondaryb-amino*tert*-butyl esters**28-31**in good yields which were subsequently treated with methanolic HCl, recrystallised and treated with saturated aqueous bicarbonate to give the mono-deprotected secondaryb-amino methyl esters**32-35**in 94-96% d.e. Deprotection of**32-35** *via*treatment with CAN afforded**36-39**in 51-61% yield. The e.e.s ofb-amino esters**36**-**39**was shown to be 94-96% by conversion to the MosherCHAR:8217s amide and comparison of the {19} F NMR spectrum of each with an authentic racemic standard (Scheme 6).

Scheme 6 *Reagents and Conditions:*(i) CAN (2.1eq), MeCN:H [2] O (5:1), RT; (ii). HCl, MeOH; (iii) recrystallisation {ethyl acetate:hexane (6:1)}; then NaHCO [3(aq)] ; (iv) CAN (4.0eq), MeCN:H [2] O (5:1).

Having demonstrated the wide applicability of this stepwise oxidative*N*-deprotection protocol for the preparation ofb-monohaloarylb-amino acid derivatives, extension to the preparation ofb-3,4-difluorophenyl-3-aminopropanoic acid**42**, an integral part of a variety of biologically active pseudo-peptides shown to exhibit potent pharmacological activity, {1} was undertaken. Thus,*tert*-butyl 3-(3,4-difluorophenyl)prop-2-enoate**40**was prepared by Wittig reaction with 3,4-difluorobenzaldehyde, giving**40**as a single diastereoisomer after recrystallisationin 88% yield. Conjugate addition of lithium amide (*R*)-**1**gave (3*S*,a*R*)-*tert*-butyl 3-(3,4-difluorophenyl-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate**41**with a crude d.e. of 90%. Recrystallisation allowed purification of (3*S*,a*R*)-**41**to 97% d.e. in 86% yield. To demonstrate the versatility of this oxidative deprotection methodology,*N*-debenzylation of both*N*-protecting groups by treatment of (3*S*,a*R*)-**41**with CAN (6eq) and subsequent treatment with aqueous acid gaveb-3,4-difluorophenyl-3-aminopropanoic acid**42**in 63% yield. The e.e. of**42**was shown to be 97% by conversion to the methyl ester, derivatisation with homochiral and racemic MosherCHAR:8217s acid chloride and subsequent {19} F NMR analysis (Scheme 7).

Scheme7: *Reagents and conditions:*(i)*tert*-butyl diethylphosphonoacetate,*n*-BuLi, THF, -78CHAR:730C; (ii). (*R*)-**1**(1.6eq), THF, -78CHAR:730C; (iii). CAN (6.0 eq), CH [3] CN/H [2] O then HCl (aq); (iv). Dowex 50W-X8.

Conclusion

In summary, the full potential of lithium*N*-benzyl-*N*-a-methyl-4-methoxybenzylamide**1**as a homochiral ammonia equivalent for the asymmetric synthesis of a range ofb-haloaryl-b-amino acid derivatives has been demonstrated. The two step deprotection protocol allows the direct isolation ofb-amino esters ready for further synthetic elaboration of the amine functionality (e.g. forb-peptide synthesis). Although only one example is given, the one step deprotection protocol is general and gives the parentb-amino acids directly. Work is currently underway directed towards transferring this versatile methodology to polymer support for the asymmetric synthesis of libraries of homochiralb-amino

acids.

General Procedure(1)

General Procedure1*n*-Butyllithium (1.05eq) was added dropwise to a stirred solution of*tert*-butyl diethylphosphonoacetate (1.1eq) in anhydrous THF at CHAR:821178CHAR:730C under N [2] and the solution left to stir for thirty minutes. The phosphonate solution was transferred*via*cannula to the aldehyde (1.0eq) in anhydrous THF at CHAR:821178CHAR:730C under Ar and the resulting solution warmed to RT over two hours. The reaction was quenched with saturated aqueous ammonium chloride (5ml), partitioned between EtOAc and H [2] O, dried and concentrated*in vacuo*. The crude product was purified by column chromatography on silica gel.

General Procedure(2)

General Procedure2*n*-Butyllithium (1.55eq) was added dropwise to a stirred solution of amine (1.6eq) in anhydrous THF at CHAR:821178CHAR:730C under N [2] and stirred for thirty minutes before addition of theb-haloaryl-a,b-unsaturated acceptor in anhydrous THF*via*cannula at CHAR:821178CHAR:730C and stirred for a further two hours. The reaction was quenched with saturated aqueous ammonium chloride (5ml) and partitioned between brine and 1:1 Et [2] O:DCM. The organic layer was washed successively with 10perc citric acid solution, saturated aqueous sodium bicarbonate solution and brine, dried and concentrated*in vacuo*. The crude product was purified by column chromatography on silica gel.

General Procedure(3)

General Procedure3CAN (2.1eq) was added to a solution of the amine (1.0eq) in 5:1 MeCN:H [2] O and the solution stirred for two hours at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et [2] O, dried and concentrated*in vacuo*. The crude product was purified by column chromatography.

General Procedure(4)

General Procedure4CAN (4.0eq) was added to a solution of the amine (1.0eq) in 5:1 MeCN:H [2] O and the solution stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et [2] O, dried and concentrated*in vacuo*. The crude product was purified by column chromatography.

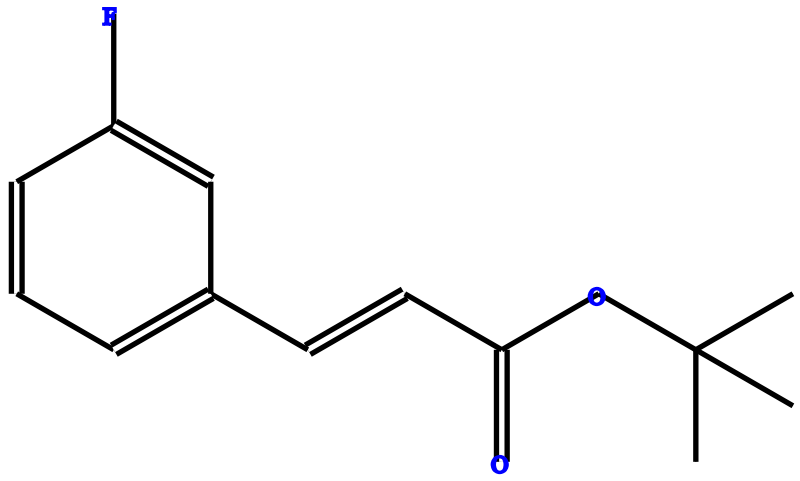
General Procedure(5)

General Procedure5Hydrogen chloride gas was bubbled through MeOH at RT for ten minutes before addition of the amine in MeOH. After two hours the reaction was concentrated*in vacuo*and the resultant solid recrystallised. After recrystallisation, the white solid was partitioned between Et [2] O and saturated aqueous sodium bicarbonate solution, dried and concentrated*in vacuo*.

Preparation of (E)-tert-butyl 3-(3-fluorophenyl)-prop-2-enoate(2)

Preparation of (*E*)-*tert*-butyl 3-(3-fluorophenyl)-prop-2-enoate2

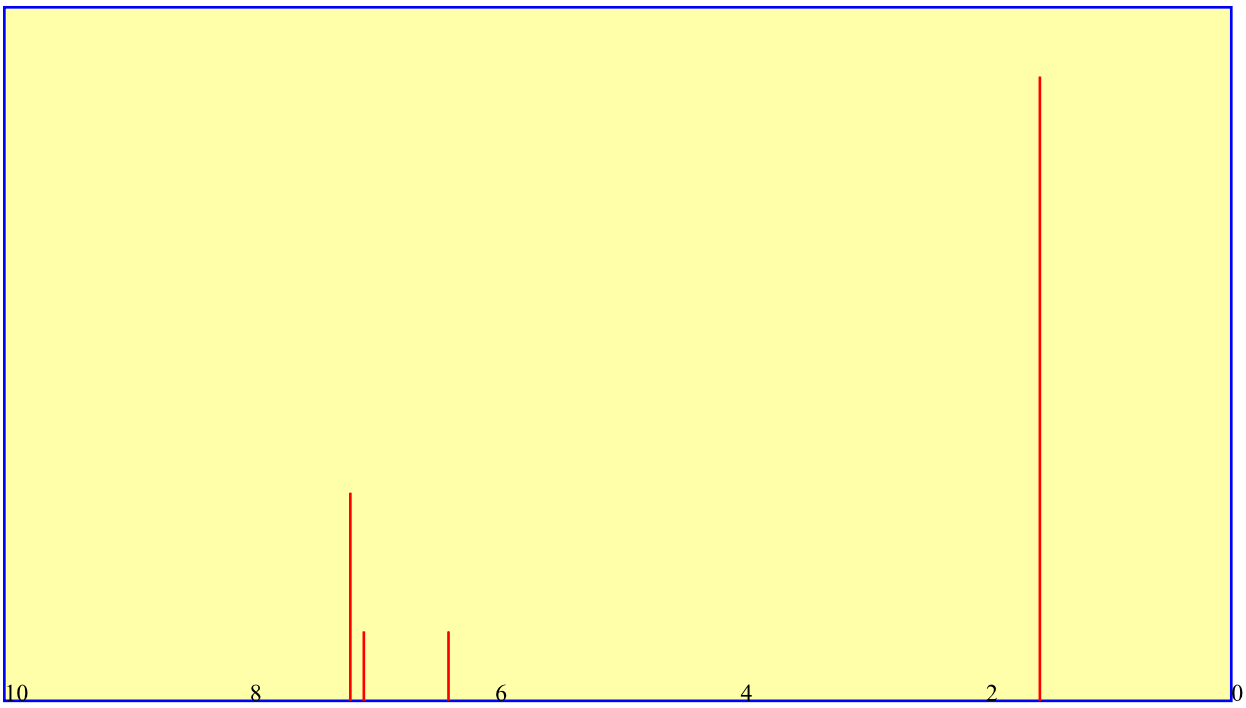
Structure:



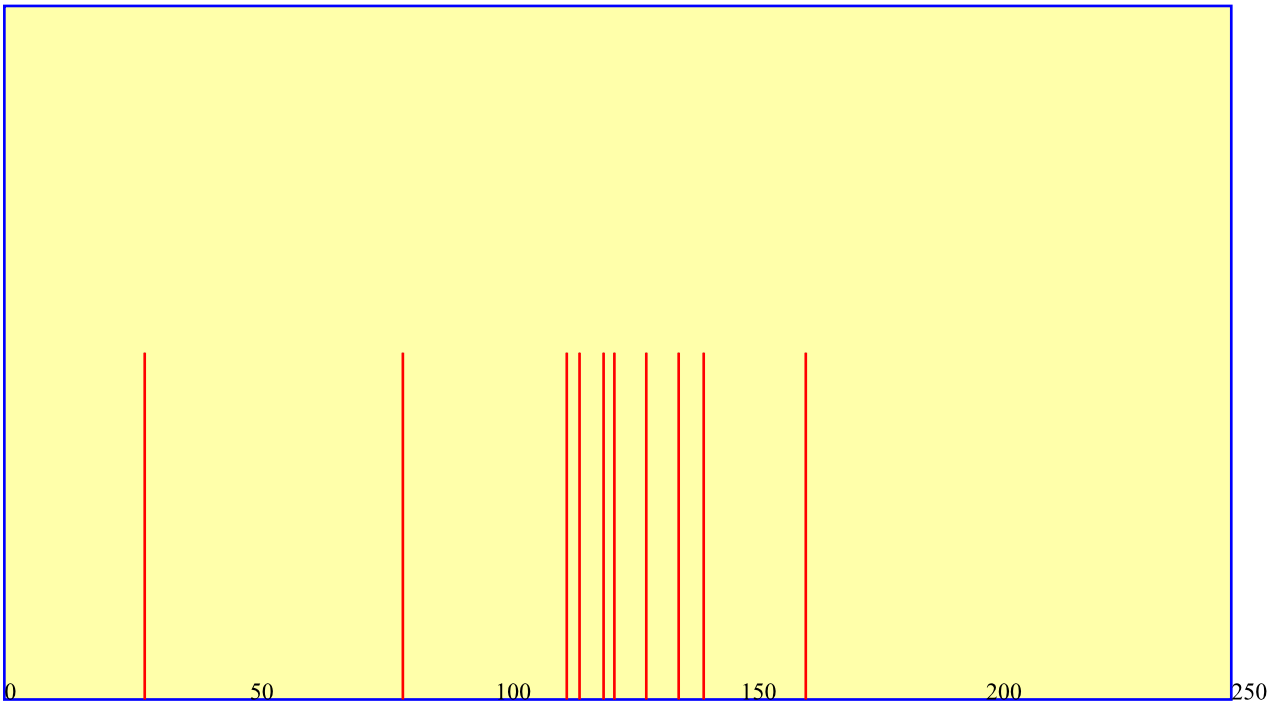
Following general procedure 1,*tert*-butyl diethylphosphonoacetate (2.73g, 10.83mmol),*n*-BuLi (2.5M 4.2ml, 10.3mmol) in THF (10ml) and 3-fluorobenzaldehyde (1.22g, 9.85mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**2**(2.01g, 92perc) as a colourless oil

IR: (film) ***()***

HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

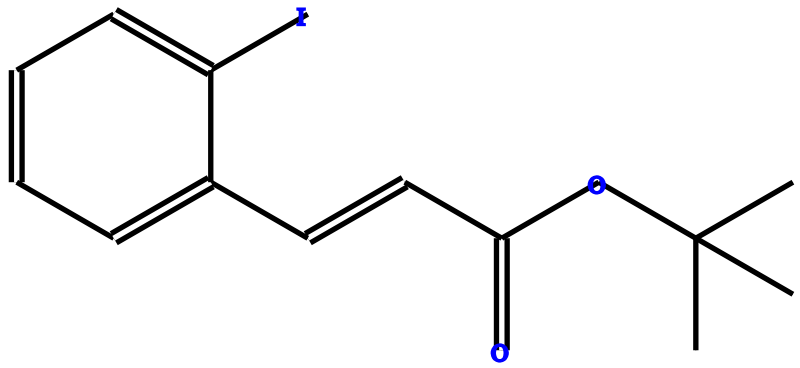


MS: CI {+} *()()*
Found:

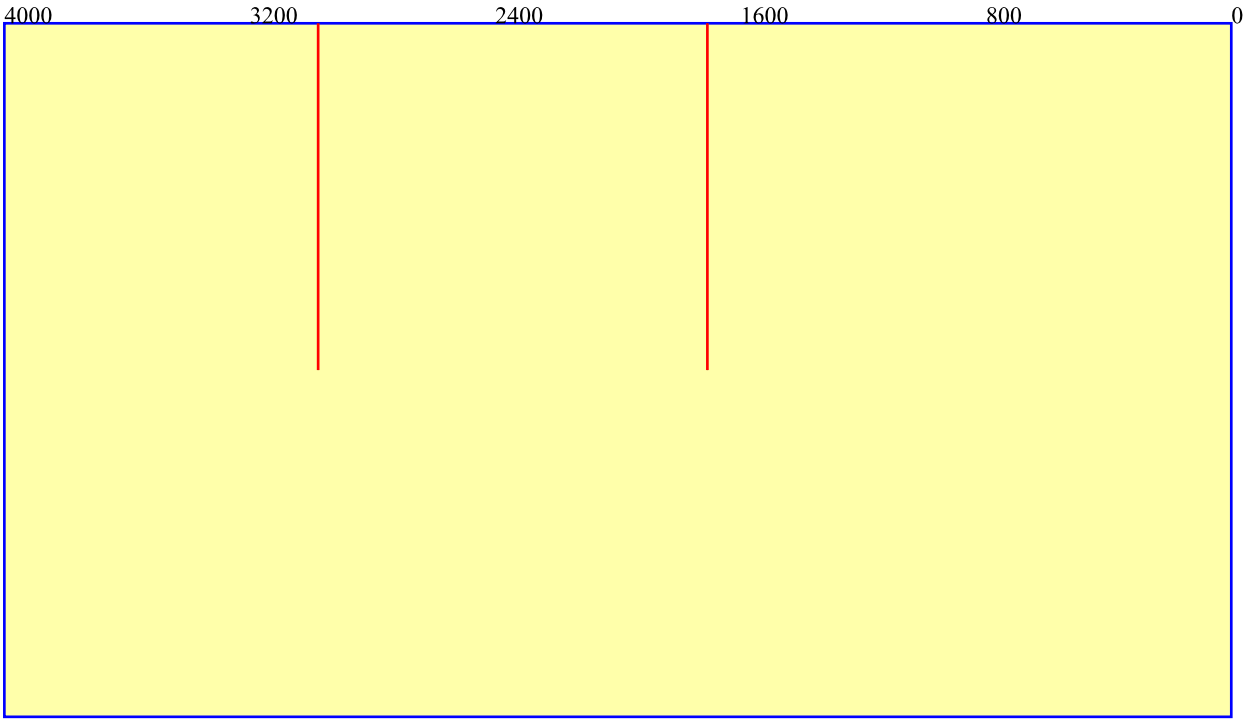
Formula:
method:
Required:
overall:

Preparation of (E)-tert-butyl 3-(2-iodophenyl)prop-2-enoate(3)

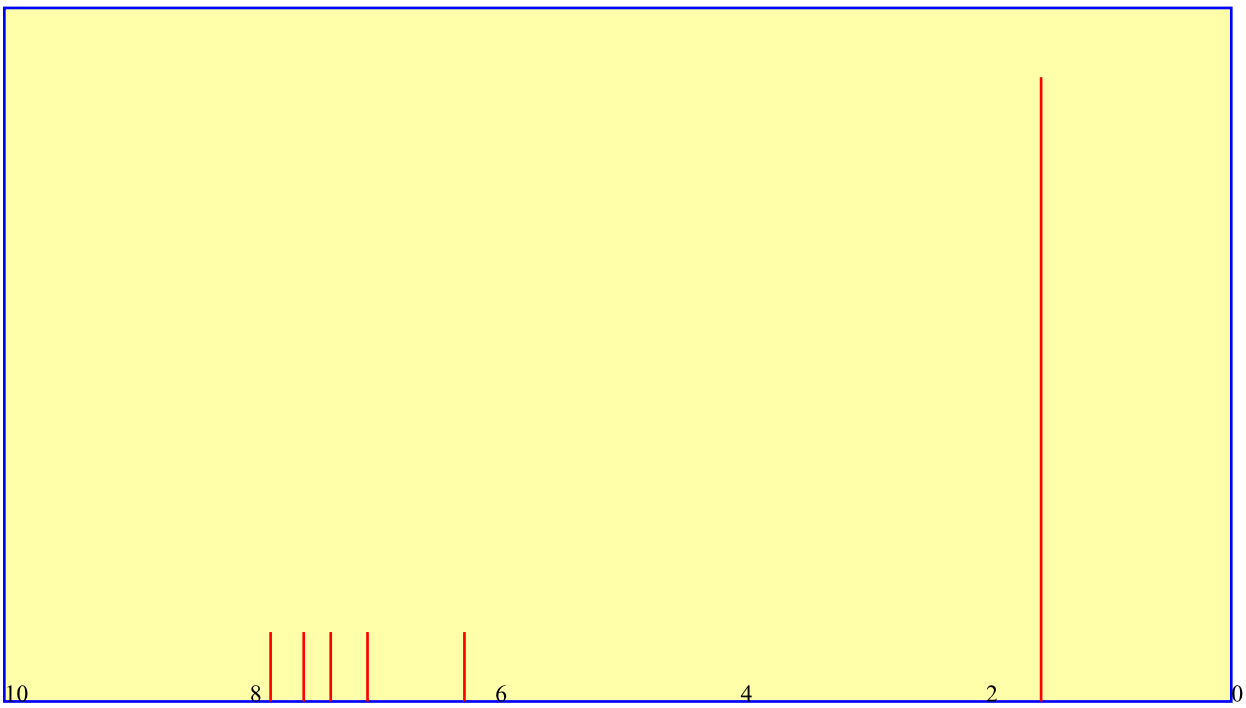
Preparation of (*E*)-*tert*-butyl 3-(2-iodophenyl)prop-2-enoate3
Structure:



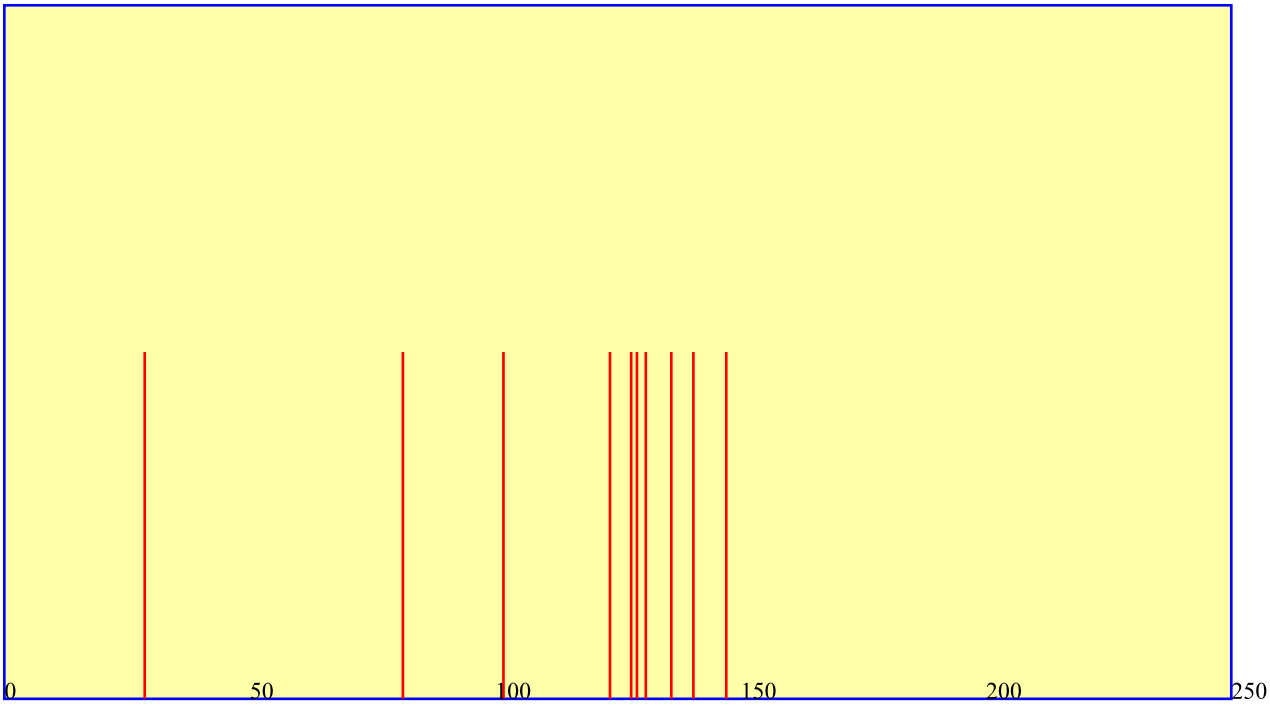
Following general procedure 1,*tert*-butyl diethylphosphonoacetate (5.0g, 19.8mmol),*n*-BuLi (1.6M 11.85ml, 19.0mmol) in THF (20ml) and 2-iodobenzaldehye (4.0g, 17.2mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**3**(5.39g, 93perc) as a yellow oil
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



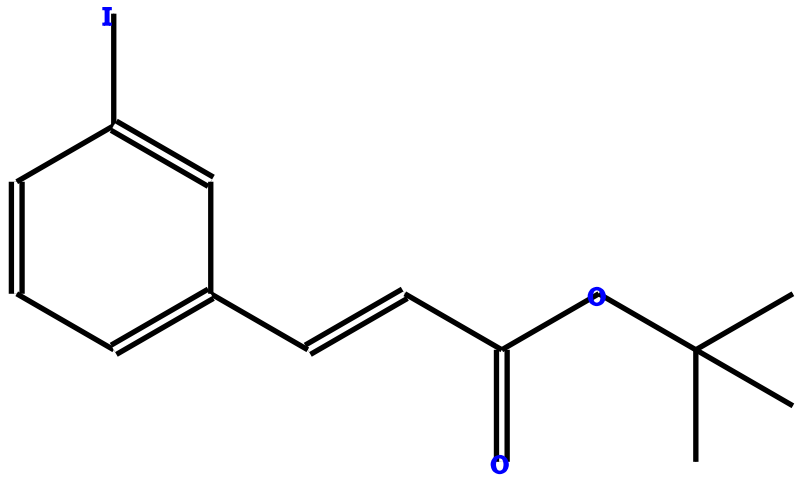
CNMR: 100 MHz *(CDCl [3])*



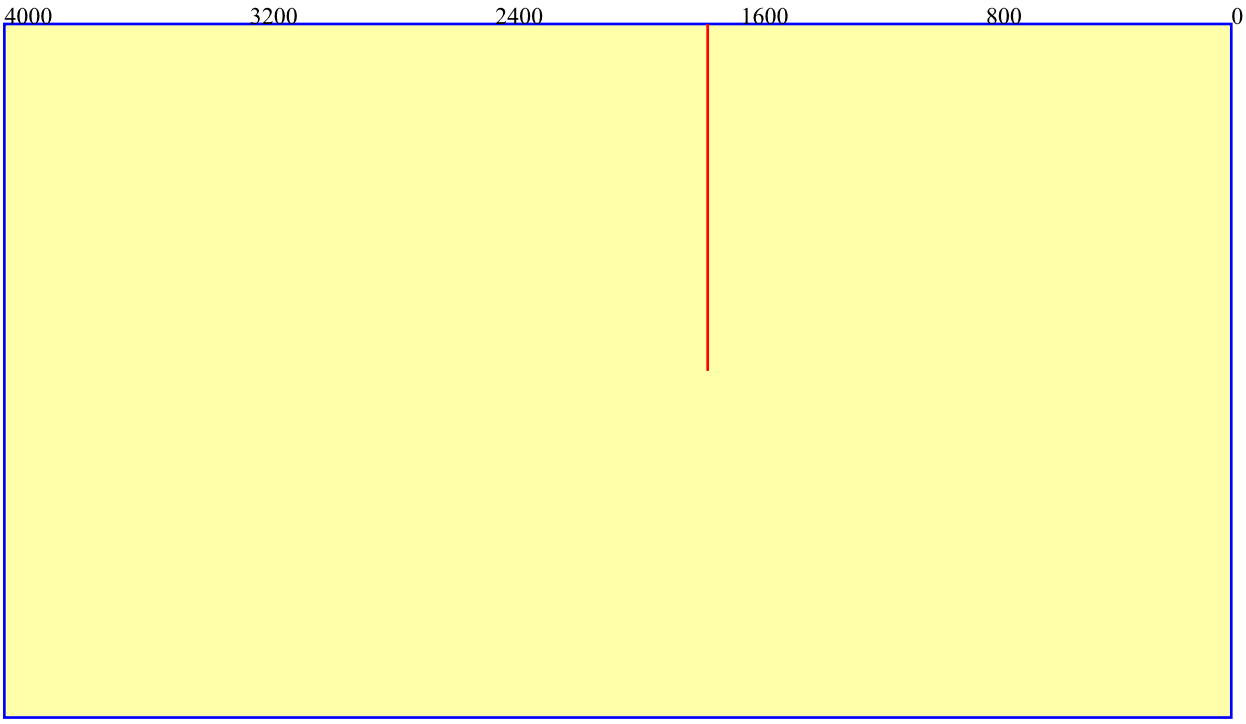
MS: CI {+} ***()()***
Found:
Formula:
method:
Required:
overall:

Preparation of (E)-tert-butyl 3-(3-iodophenyl)prop-2-enoate(4)

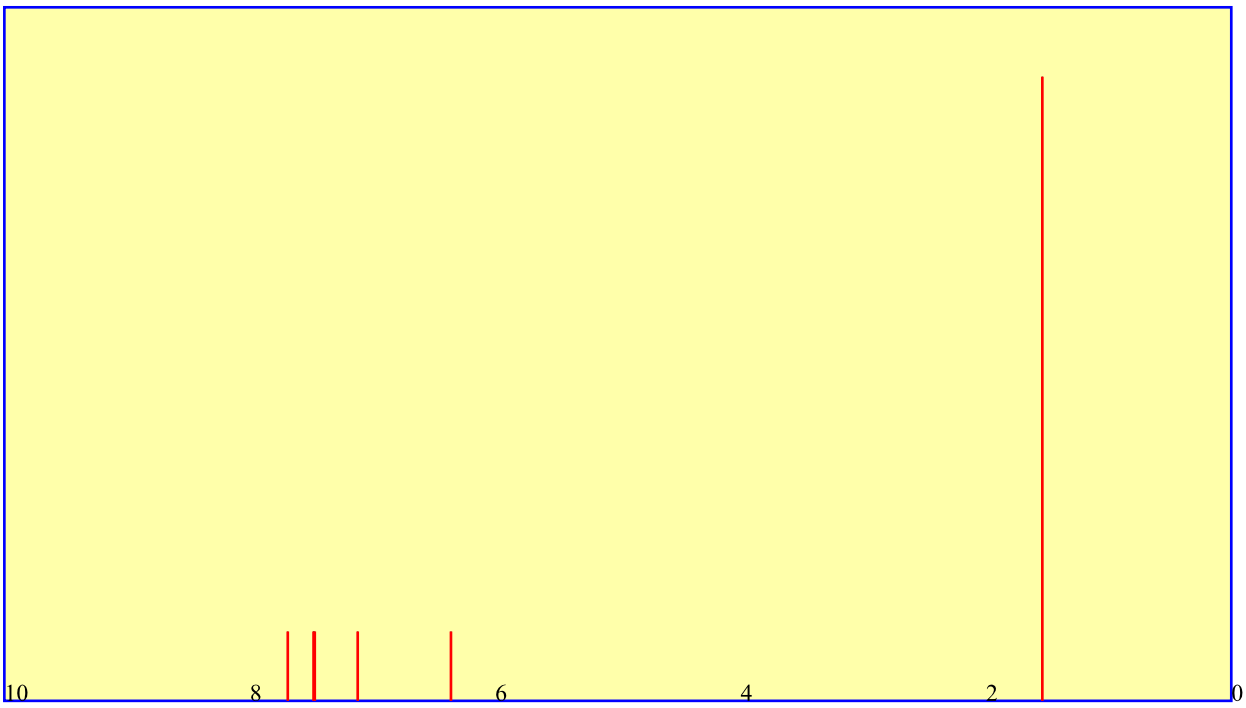
Preparation of (*E*)-*tert*-butyl 3-(3-iodophenyl)prop-2-enoate4
Structure:



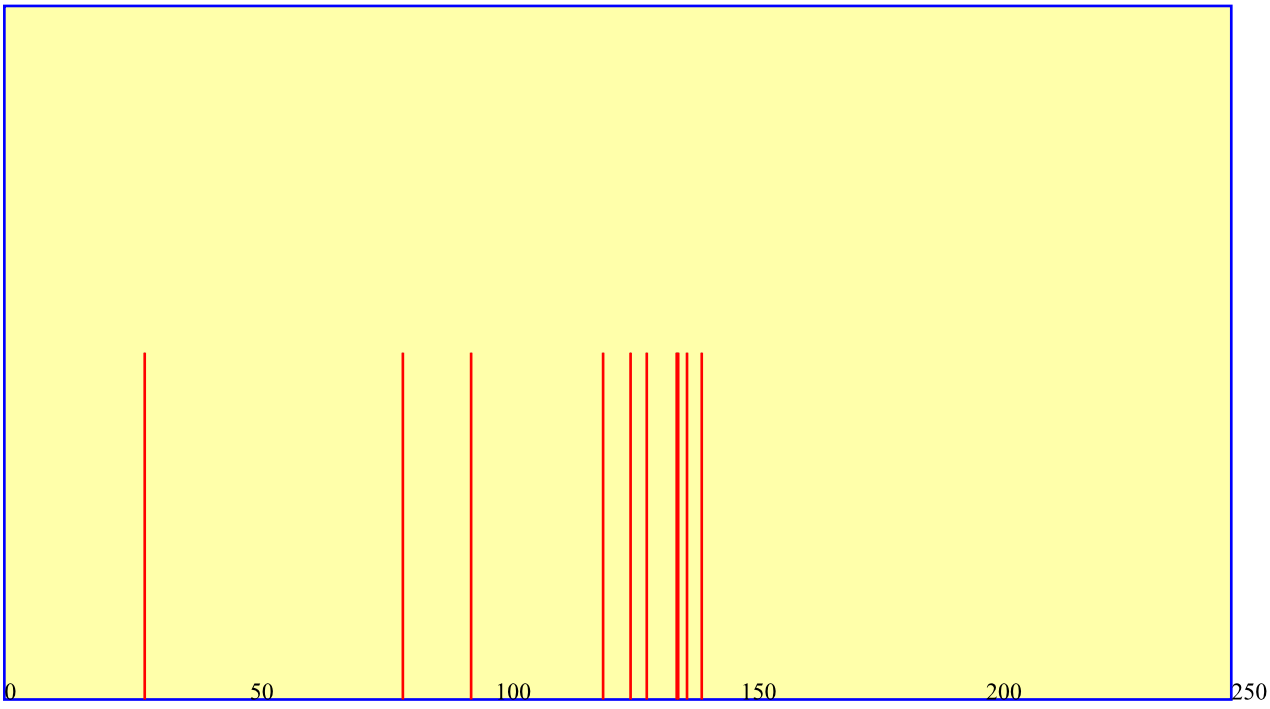
Following general procedure 1,*tert*-butyl diethylphosphonoacetate (4.1g, 16.3mmol),*n*-BuLi (2.5M 6.2ml, 15.5mmol) in THF (15ml) and 3-iodobenzaldehye (3.43g, 14.8mmol) in THF (15ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**4**(4.15g, 85perc) as a yellow oil.
IR: (film) ***()***



HNMR: 400 MHz *(CDCl [3])*

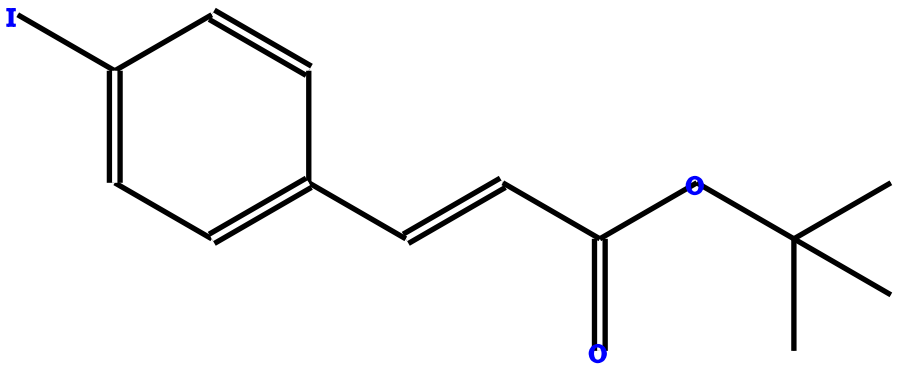


CNMR: 100 MHz *(CDCl [3])*

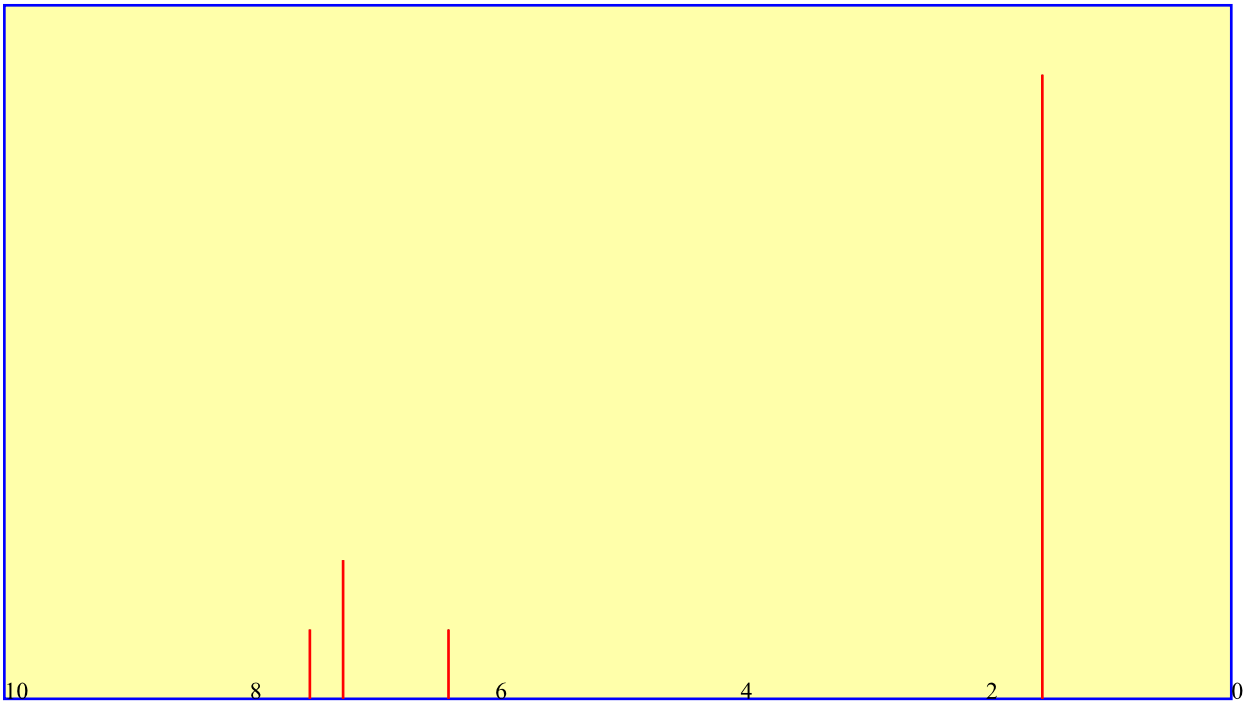


MS: CI {+} *()()*
Found:

Formula:
method:
Required:
overall:
Preparation of (*E*)-*tert*-butyl 3-(4-iodophenyl)prop-2-enoate {11} **5**
Structure:



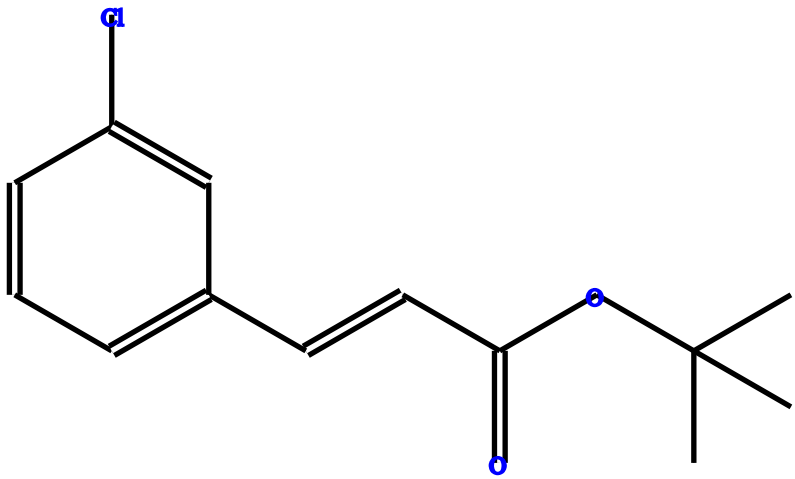
Following general procedure 1,*tert*-butyl diethylphosphonoacetate (3.9g, 15.5mmol),*n*-BuLi (2.5M 9.25ml, 14.8mmol) in THF (20ml) and 4-iodobenzaldehye (3.1g, 13.5mmol) in THF (20ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1) and recrystallization (hexane:Et [2] O),**5**(4.2g, 94perc) as white needles; mp. 65-66C (hexane:Et [2] O)
HNMR: 400 MHz *(CDCl [3])*



Preparation of (E)-tert-butyl 3-(3-chlorophenyl)prop-2-enoate(6)

Preparation of (*E*)-*tert*-butyl 3-(3-chlorophenyl)prop-2-enoate6

Structure:

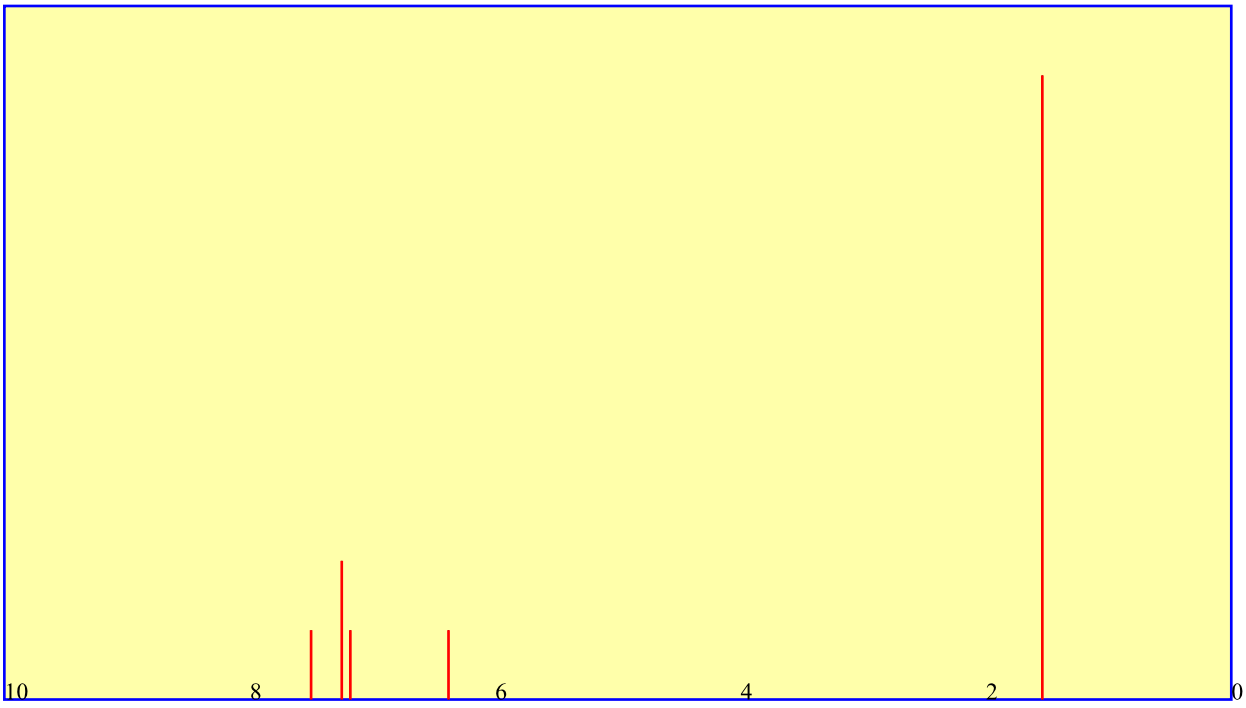


Following general procedure 1,*tert*-butyl diethyl phosphonoacetate (5.9g,

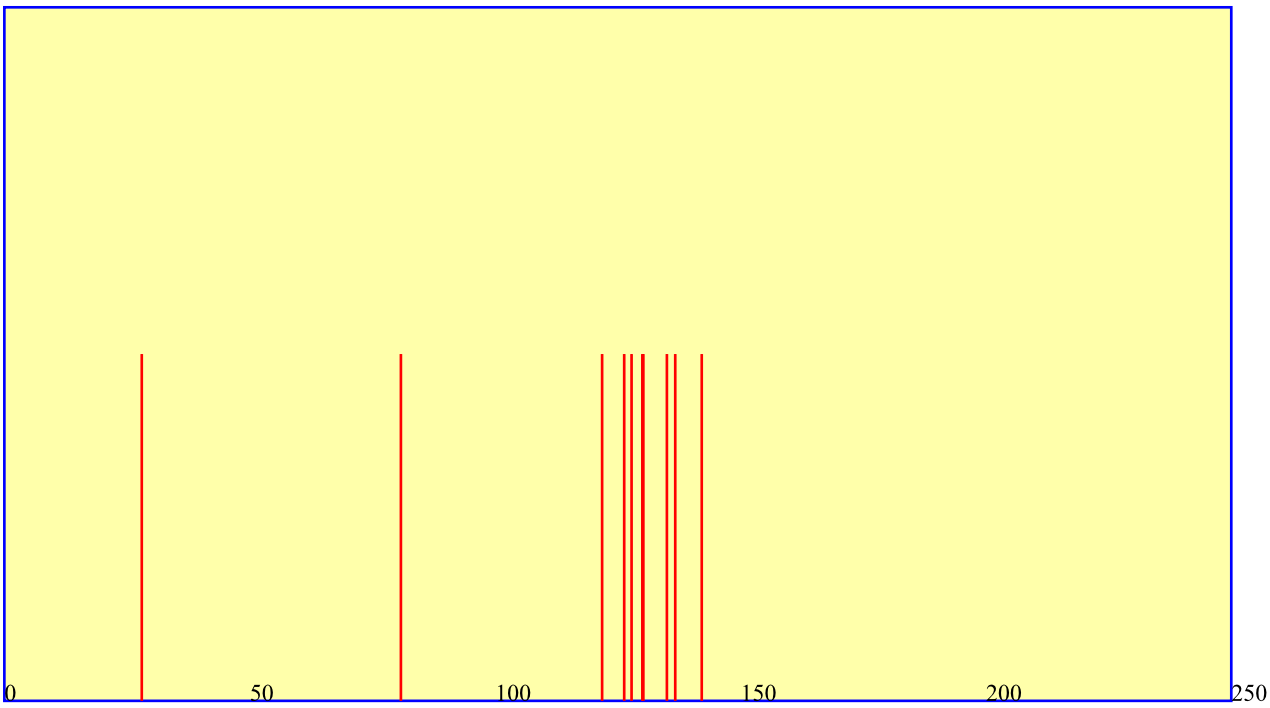
n-BuLi (2.5M 9.0ml, 22.5mmol) in THF (15ml) and 3-chlorobenzaldehyde (3.0g, 21.4mmol) in THF (15ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**6**(4.69g, 92perc) as a colourless oil

IR: (film) ***()***

HNMR: 400 MHz ***(CDCl [3])***



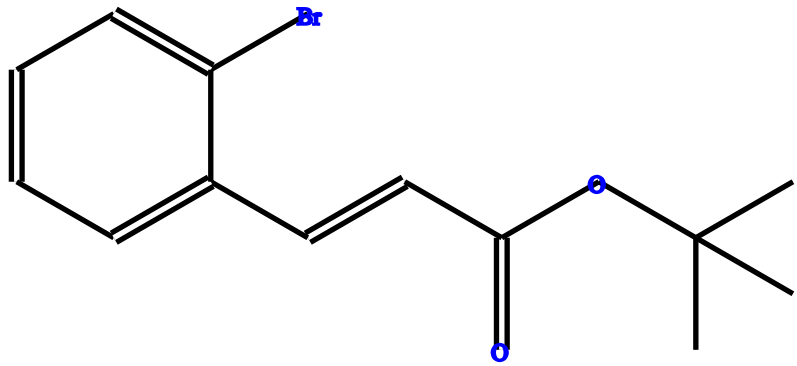
CNMR: 100 MHz *(CDCl [3])*



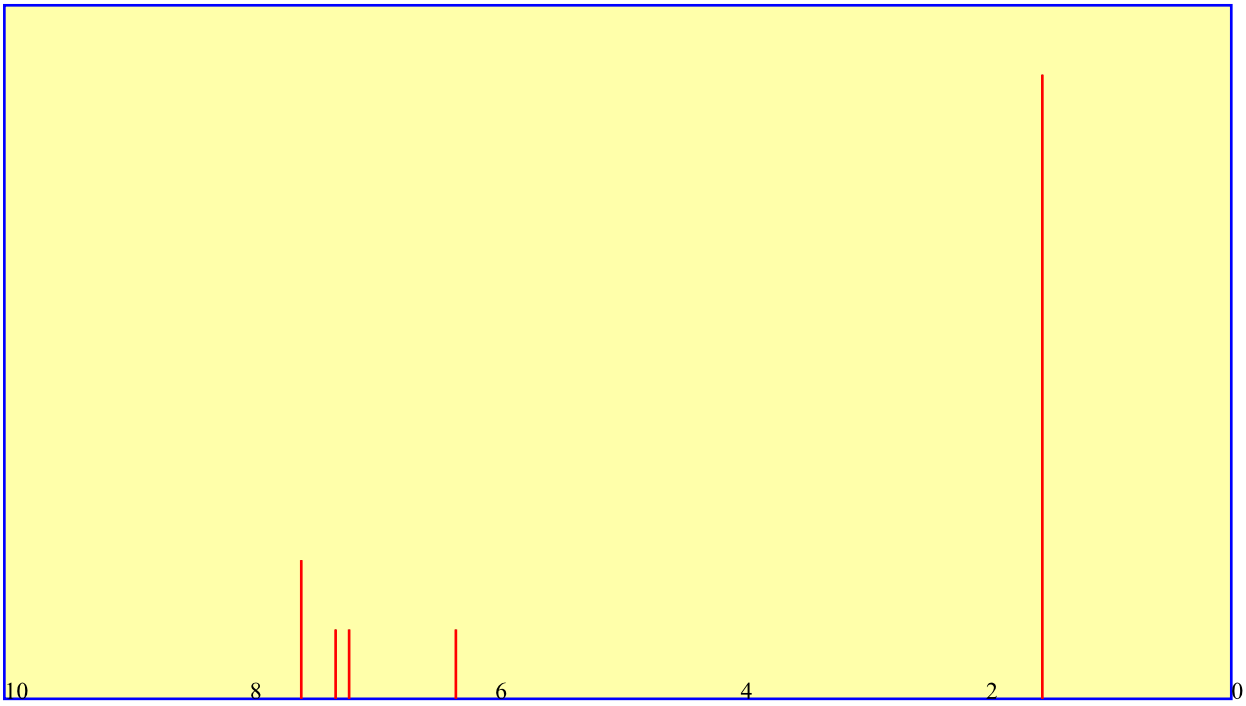
MS: CI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (E)-tert-butyl 3-(2-bromophenyl)prop-2-enoate(7)

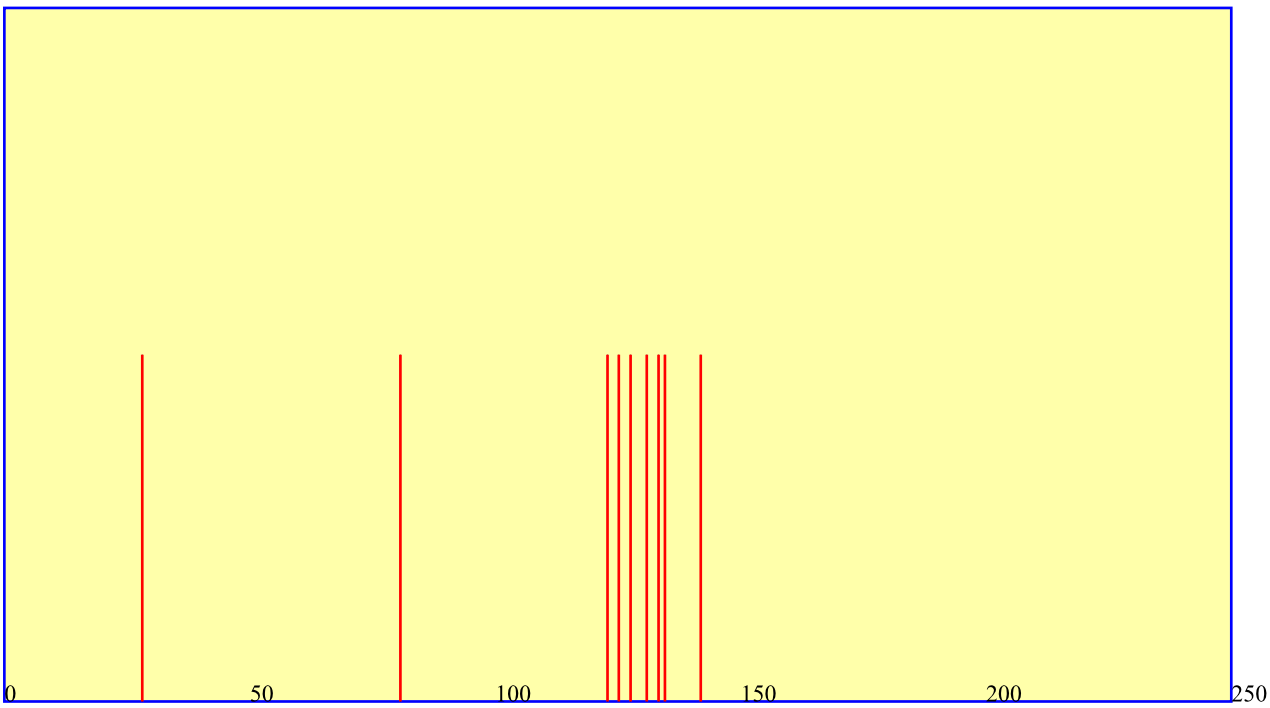
Preparation of (*E*)-*tert*-butyl 3-(2-bromophenyl)prop-2-enoate7
Structure:



Following general procedure 1,*tert*-butyl diethyl phosphonoacetate (5.8g, 23.1mmol),*n*-BuLi (2.5M 9.25ml, 21.1mmol) in THF (20ml) and 2-bromobenzaldehyde (3.3g, 17.8mmol) in THF (20ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**7**(4.7g, 93perc) as a colourless oil;u [max] (film) 1710 (C=O), 1635 (C=C)
HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

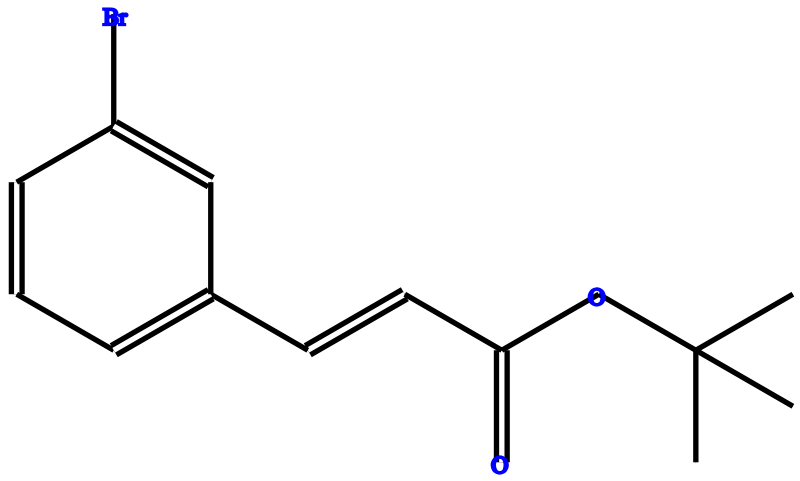


MS: CI {+} *()()*
Found:
Formula:

method:
Required:
overall:

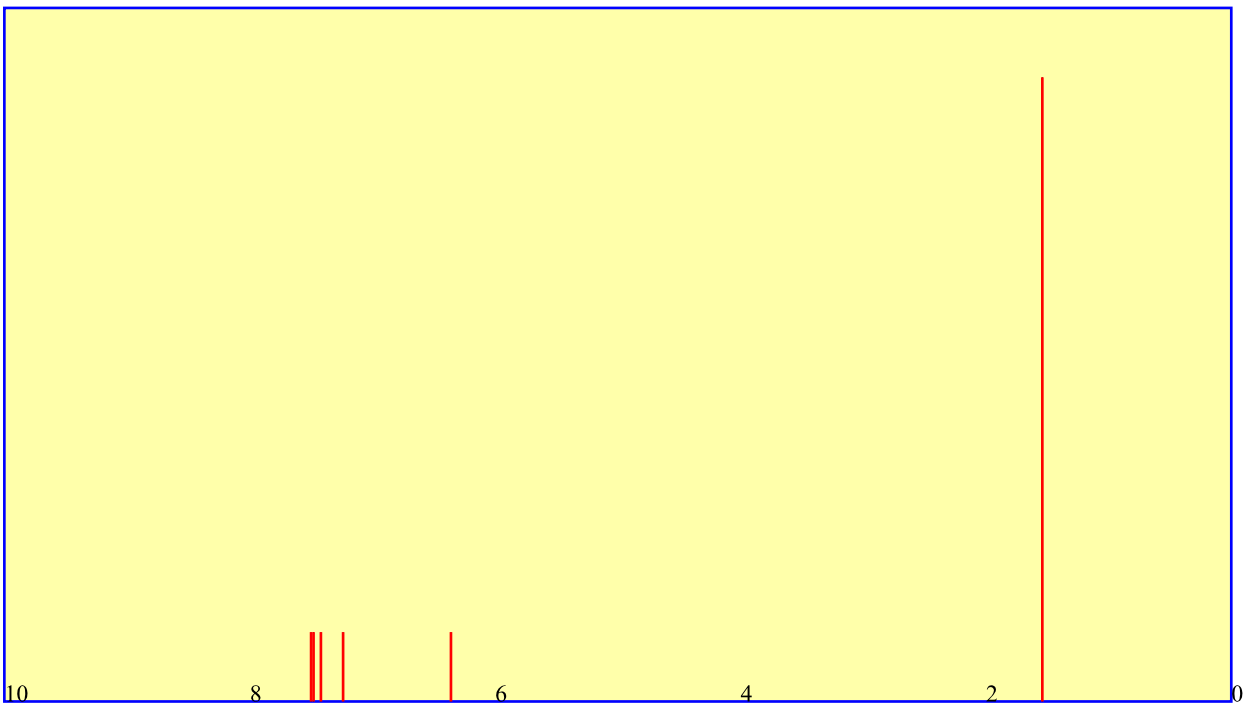
Preparation of (E)-tert-butyl 3-(3-bromophenyl)prop-2-enoate(8)

Preparation of (*E*)-*tert*-butyl 3-(3-bromophenyl)prop-2-enoate8
Structure:

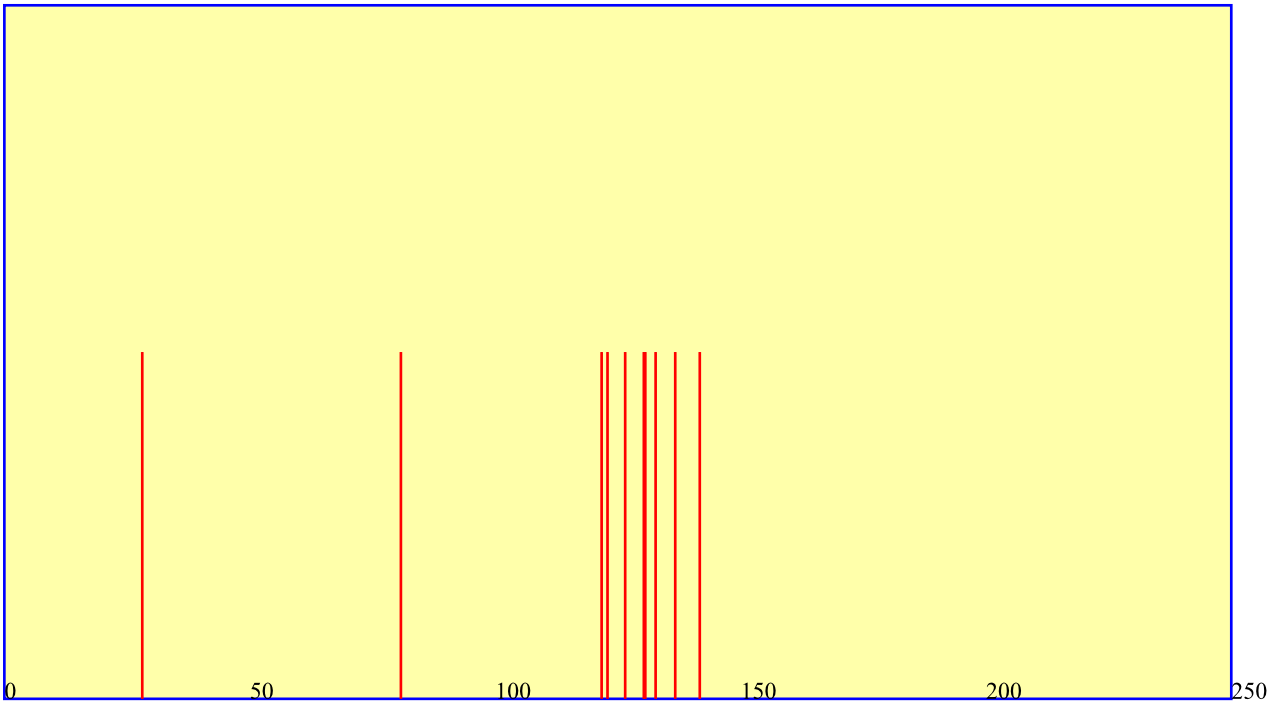


Following general procedure 2,*tert*-butyl diethyl phosphonoacetate (1.5g, 5.94mmol),*n*-BuLi (2.5M 2.27ml, 5.67mmol) in THF (10ml) and 3-bromobenzaldehyde (1.0g, 5.40mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**8**(1.3g, 85perc) as a colourless oil
IR: (film) *()*

HNMR: 400 MHz *(CDCl [3])*



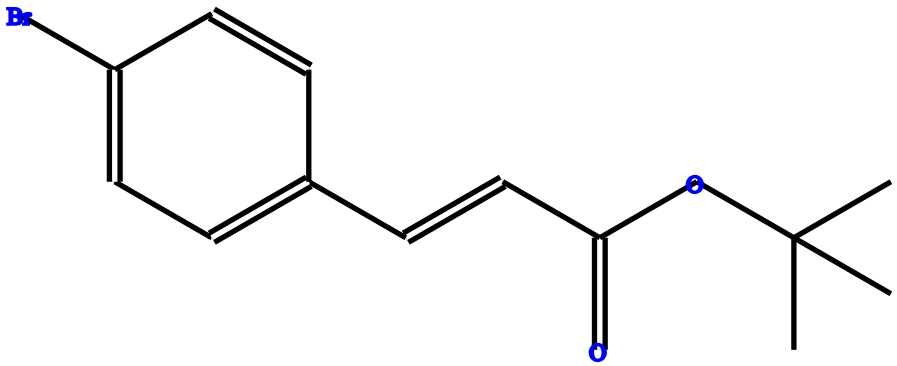
CNMR: 100 MHz *(CDCl [3])*



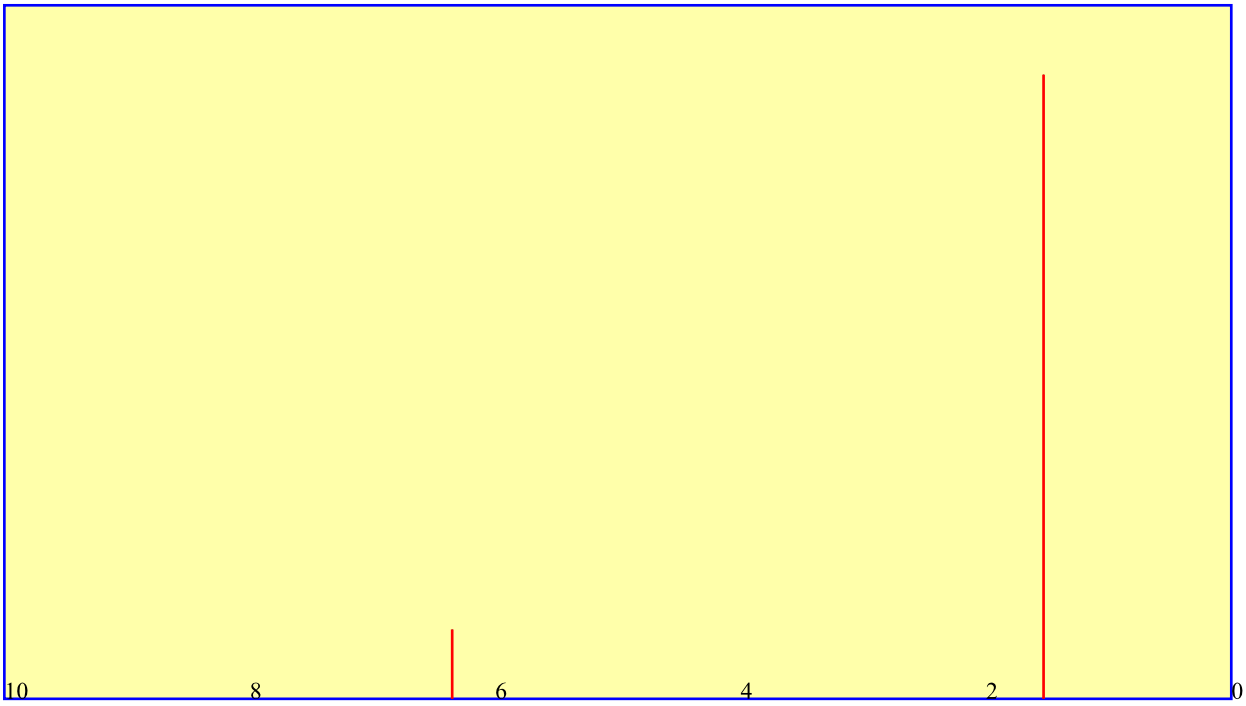
MS: CI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (E)-tert-butyl 3-(4-bromophenyl)-prop-2-enoate(9)

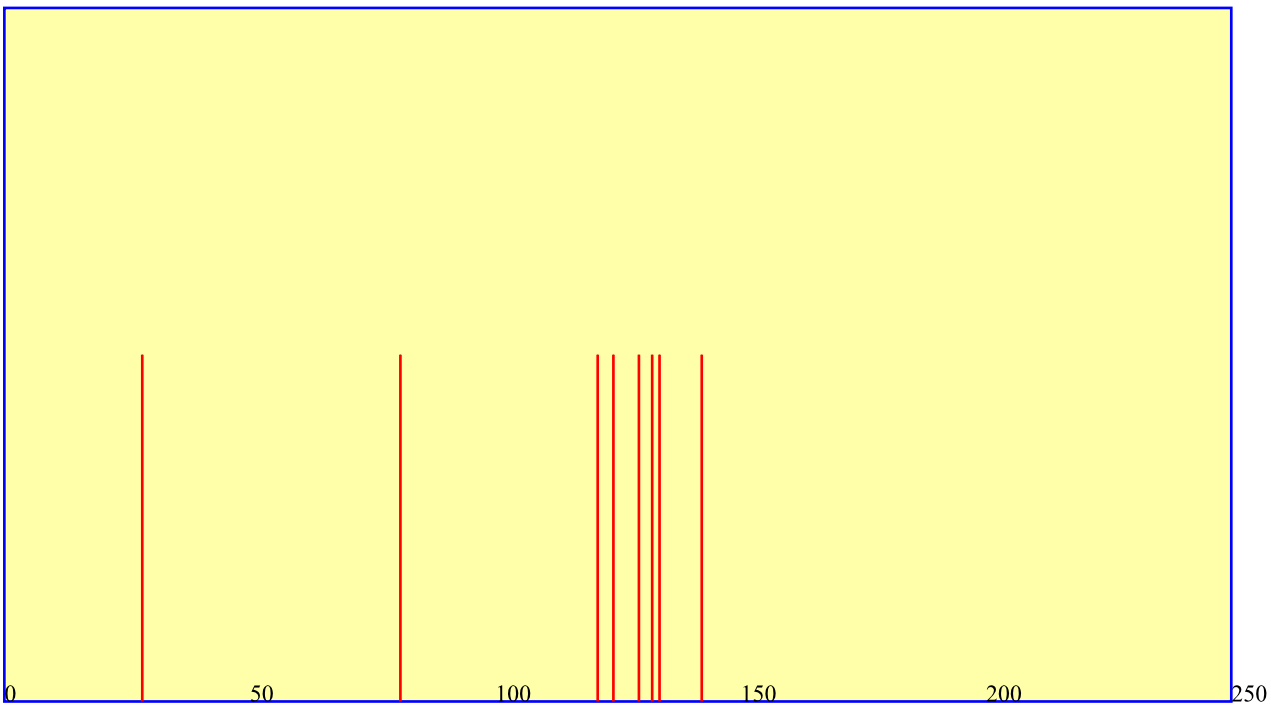
Preparation of (*E*)-*tert*-butyl 3-(4-bromophenyl)-prop-2-enoate9
Structure:



Following general procedure 1,*tert*-butyl diethylphosphonoacetate (2.7g, 10.9mmol),*n*-BuLi (2.5M 4.2ml, 10.3mmol) in THF (10ml) and 4-bromobenzaldehyde (1.2g, 9.9mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 40:1),**9**(2.0g, 92perc) as white needles; m.p. 66CHAR:730C (hexane:Et [2] O); Found C, 55.3perc, H, 5.1perc; C [13] H [15] BrO [2] requires C, 55.15perc, H, 5.3perc;*v* [max] (KBr) 1707 (C=O), 1637 (C=C)
HNMR: 400 MHz *(CDCl [3])*



CNMR: 50 MHz *(CDCl [3])*



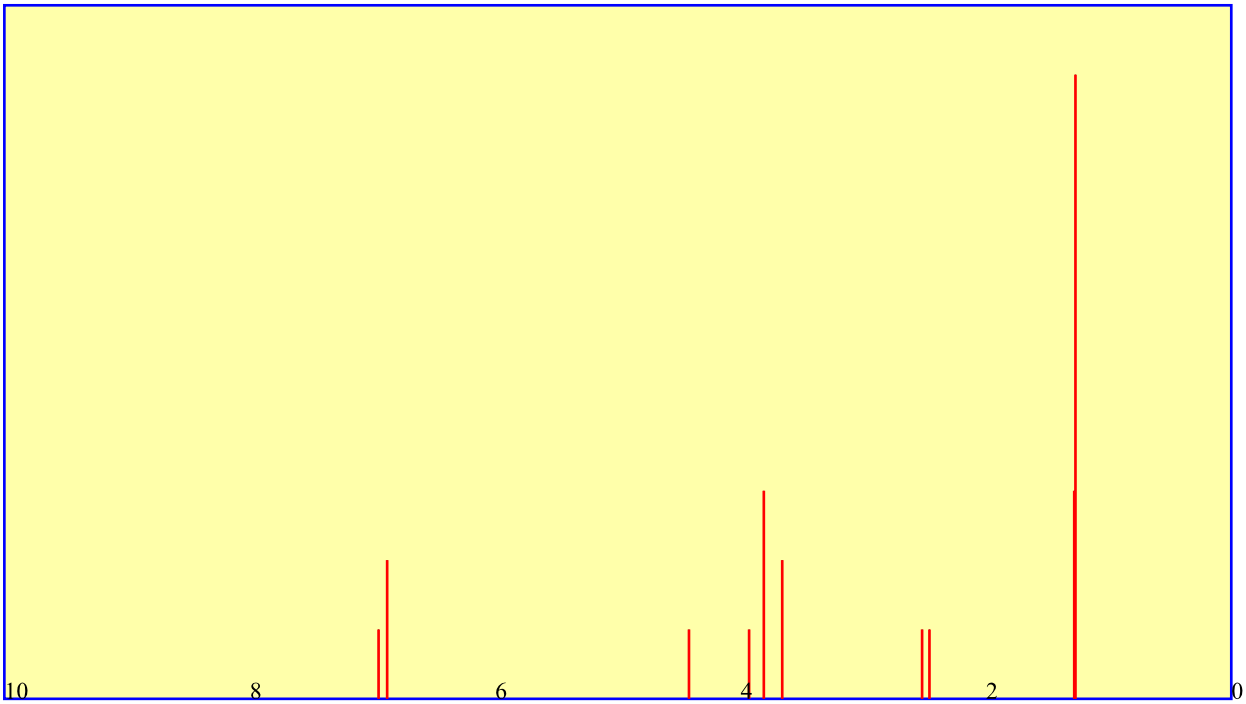
MS: NH [3] *()()*
Found:
Formula:

method:
Required:
overall:

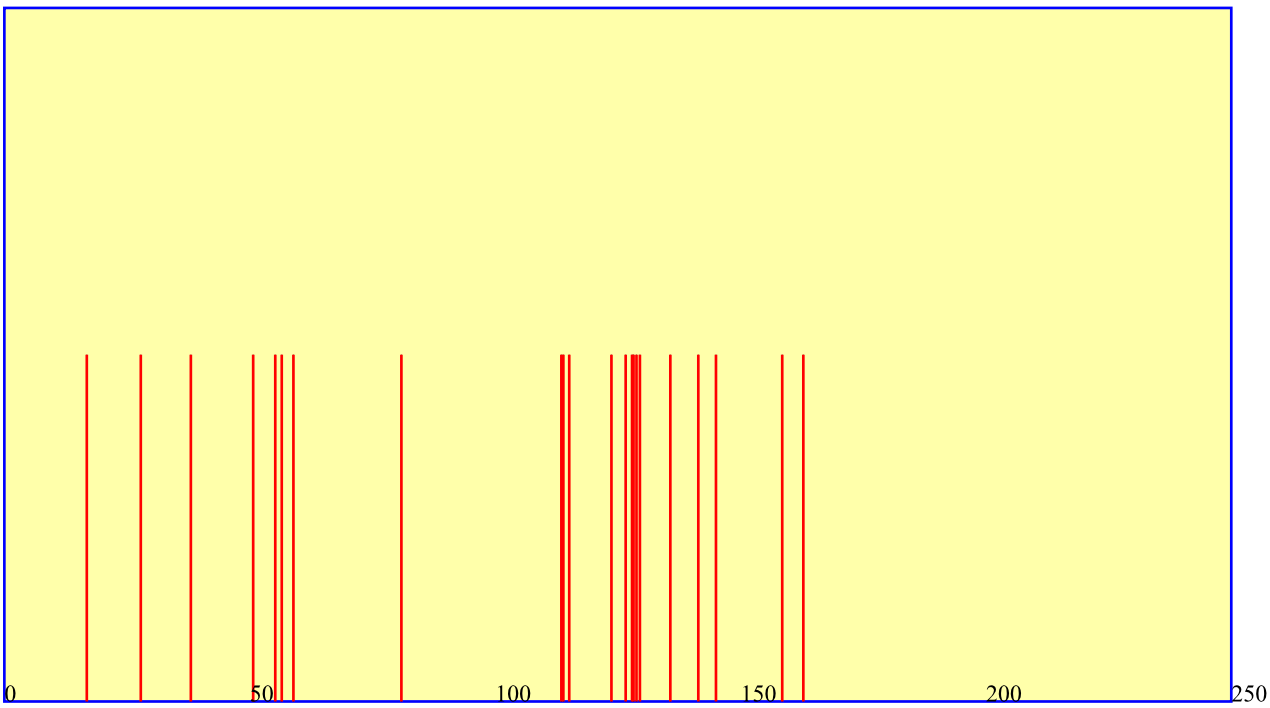
Preparation of (3R,aS)-tert-butyl 3-(3-fluorophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(10)

Preparation of (3*R*,a*S*)-*tert*-butyl 3-(3-fluorophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate10Following general procedure 2,*n*-BuLi (2.5M 2.8ml, 7.0mmol), (*S*)-*N*-a-methyl-*N*-4-methoxybenzylamine (1.74g, 7.2mmol) in THF (10ml) and (*E*)-**2**(1.0g, 4.5mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 10:1) and recrystallisation (hexane:Et [2] O),**10**(1.60g, 77perc) as a white solid; Found: C, 75.2; H, 7.3; N 3.0perc; C [29] H [34] FNO [3] requires C, 75.1; H, 7.4; N, 3.0perc; mp 87-88C (hexane:Et [2] O)
OR: [a]D= (*c*,)
IR: (KBr disc) *()*

HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*



MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

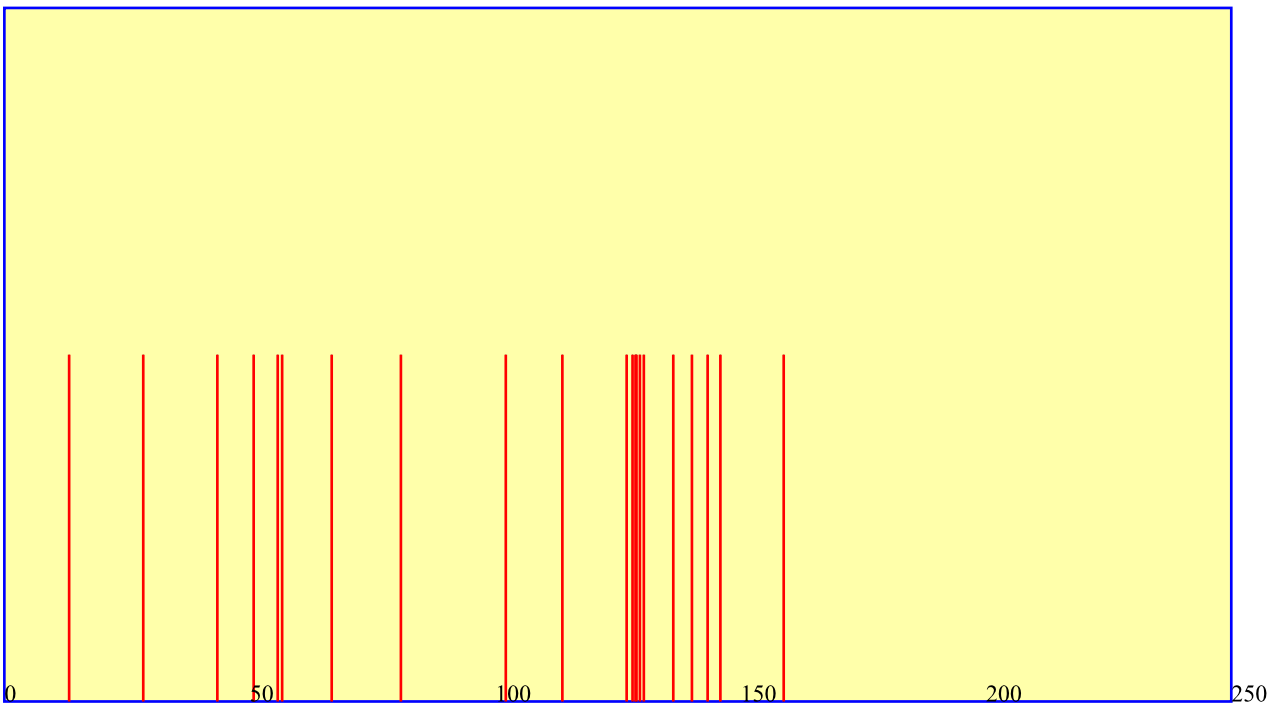
Preparation of (3R,aS)-tert-butyl 3-(2-iodophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(11)

Preparation of (3*R*,a*S*)-*tert*-butyl 3-(2-iodophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate11Following general procedure 2,*n*-BuLi (2.5M 1.88ml, 4.7mmol), (*S*)-*N*-a-methyl-*N*-4-methoxybenzylamine (1.17g, 4.9mmol) in THF (10ml) and (*E*)-**3**(1.0g, 3.0mmol) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 15:1) and recrystallisation (hexane:Et [2] O),**11**(1.32g, 76perc) as white crystals; mp 98-99C (hexane:Et [2] O); Found: C, 61.1; H, 6.05; N, 2.5perc; C [29] H [34] INO [3] requires C, 60.95; H, 6.0; N, 2.45perc OR: [a]D= (*c*,)

IR: (film) ***()***

HNMR: 400 MHz ***(CDCl [3])***

CNMR: 100 MHz *(CDCl [3])*

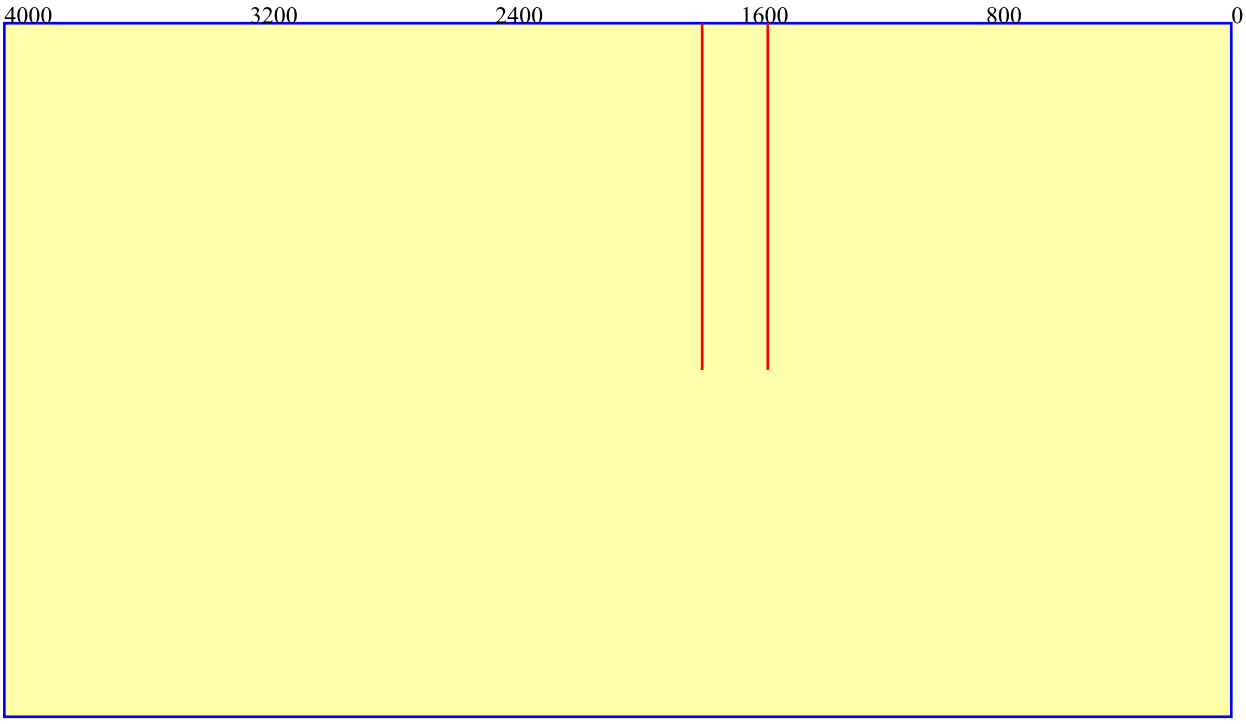


MS: APCI {+} *()()*
Found:
Formula:

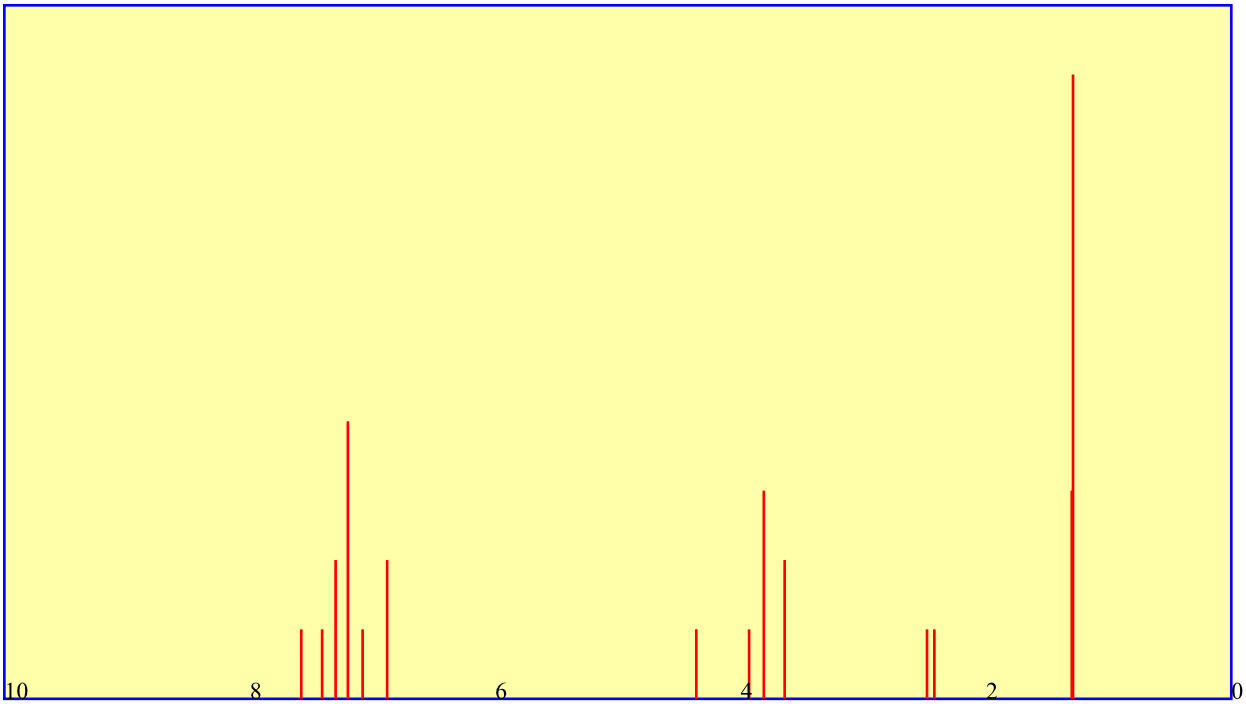
method:
Required:
overall:

Preparation of (3R,aS)-tert-butyl 3-(3-iodophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(12)

Preparation of (3*R*,a*S*)-*tert*-butyl 3-(3-iodophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate12Following general procedure 2,*n*-BuLi (2.5M 3.9ml, 9.7mmol), (*S*)-*N*-a-methyl-*N*-4-methoxybenzylamine(2.26g, 9.4mmol) in THF (20ml) at -78C and (*E*)-**4**(2.0g, 6.06mmol) in THF (20ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 15:1),**12**(2.56g, 74perc) as a pale green oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



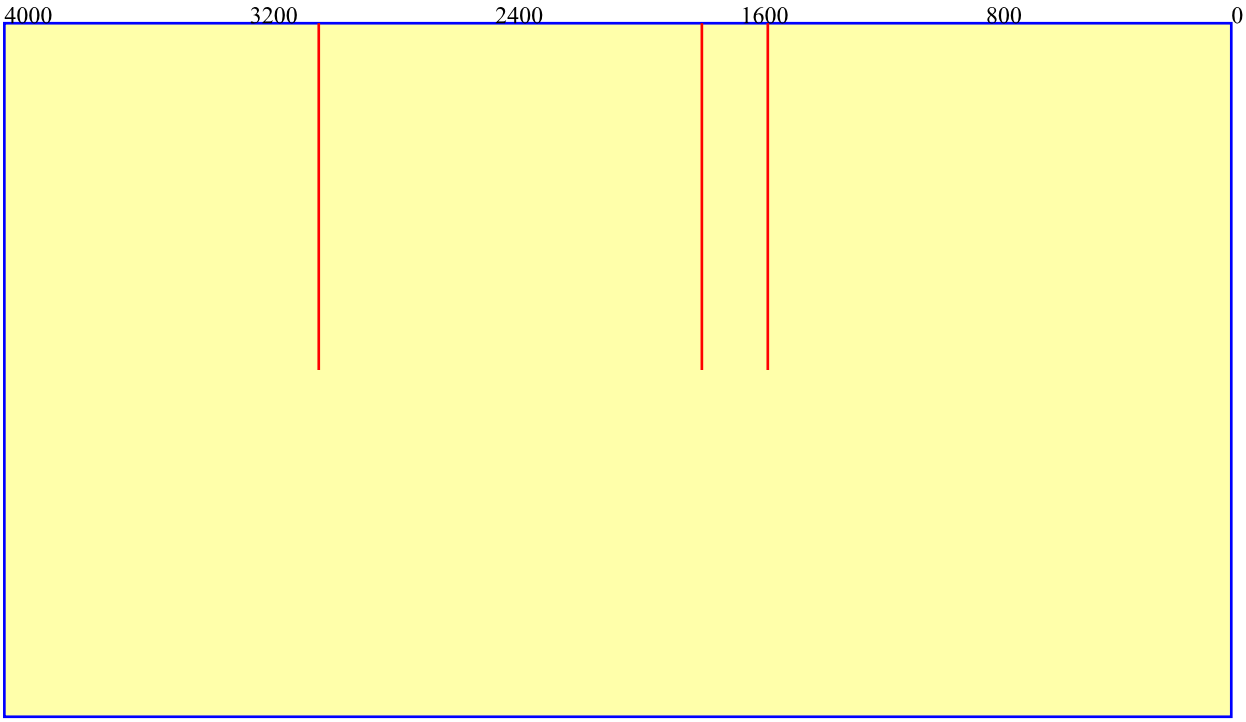
CNMR: 100 MHz *(CDCl [3])*

MS: APCI {+} *()()*
Found:
Formula:

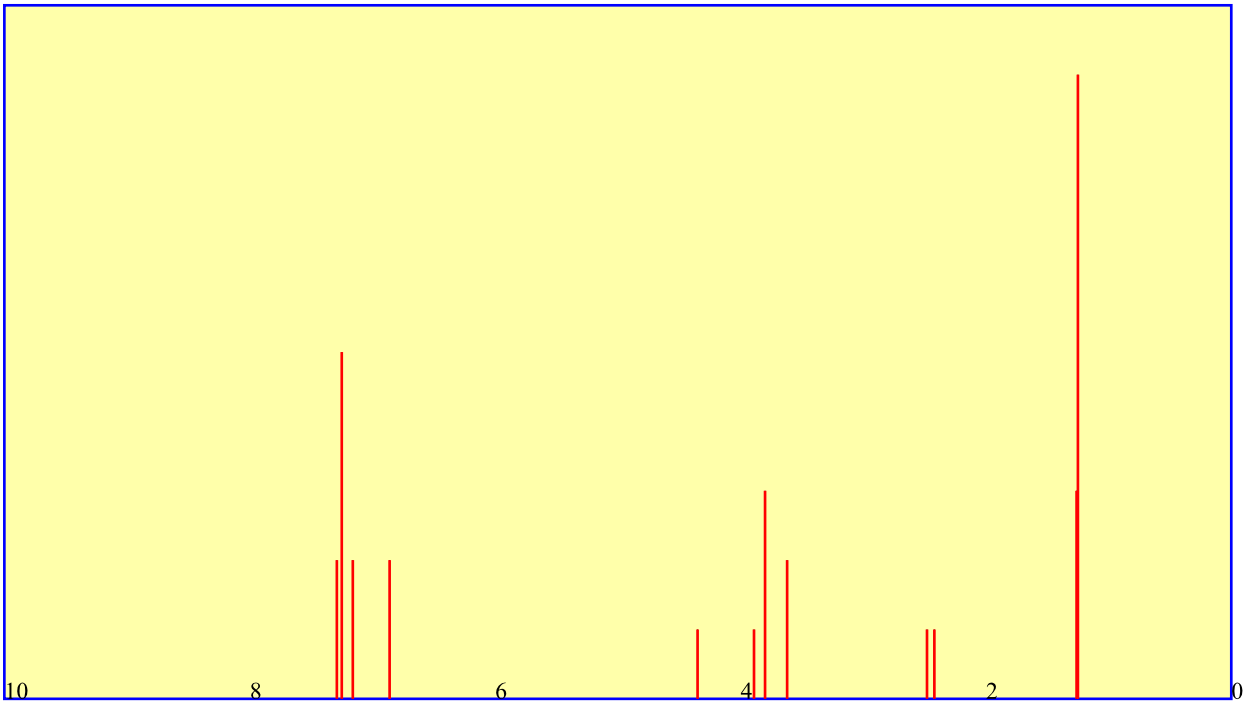
method:
Required:
overall:

Preparation of (3R,aS)-tert-butyl 3-(4-iodophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(13)

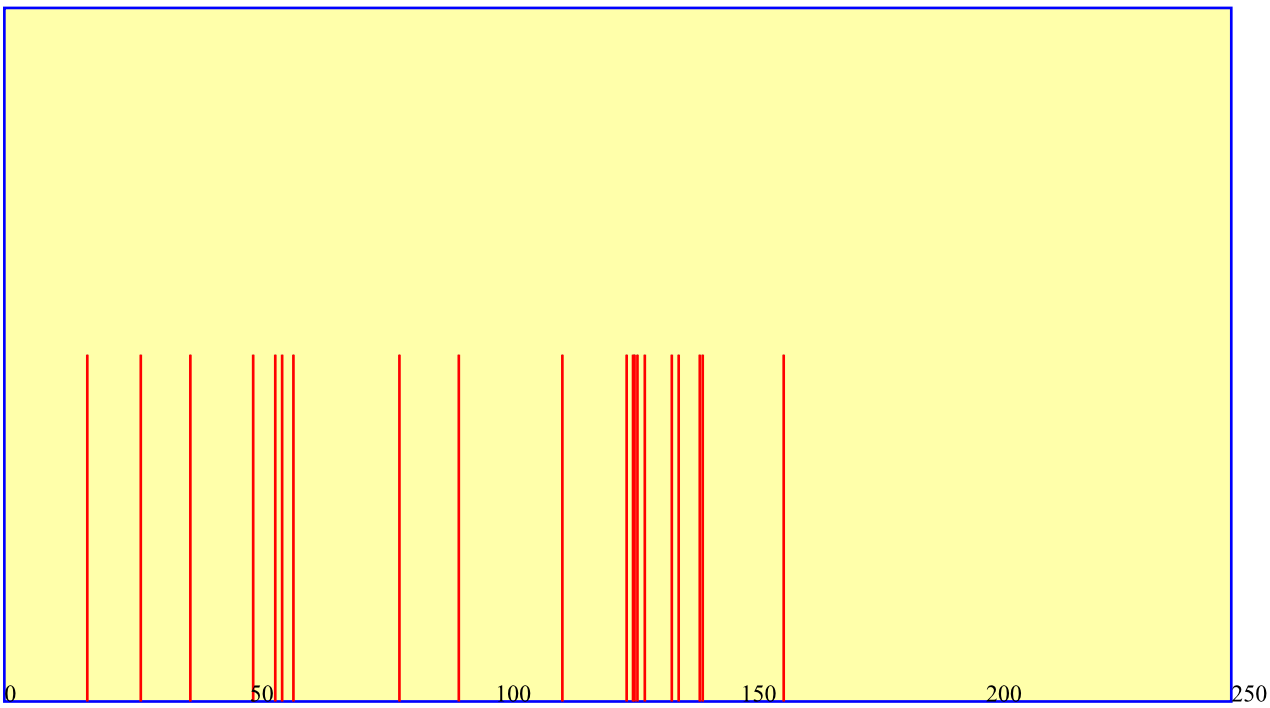
Preparation of (3*R*,a*S*)-*tert*-butyl 3-(4-iodophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate13Following general procedure 2,*n*-BuLi (2.5M 2.2ml, 5.4mmol), (*S*)-*N*-a-methyl-*N*-4-methoxybenzylamine(1.27g, 5.25mmol) in THF (15ml) and (*E*)-**5**(1.12g, 3.4mmol) in THF (15ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 15:1),**13**(1.53g, 79perc) as a white foam
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*



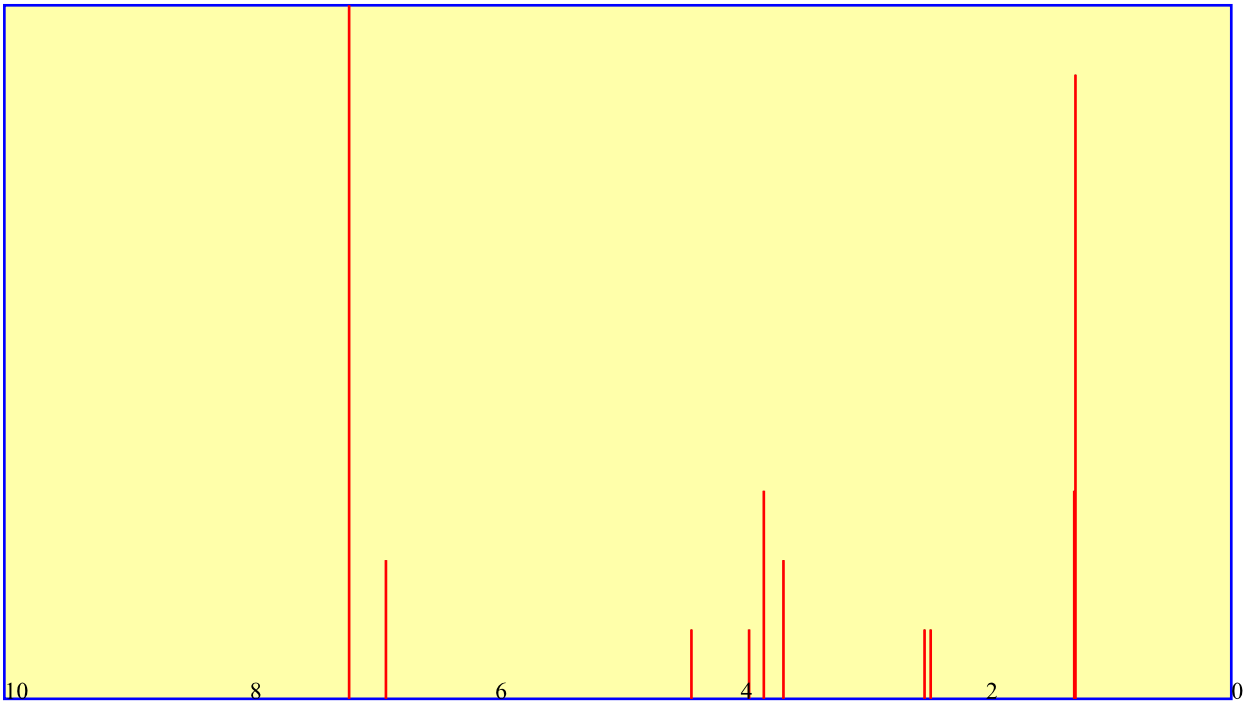
MS: CI {+} *()()*
Found:
Formula:

method:
Required:
overall:

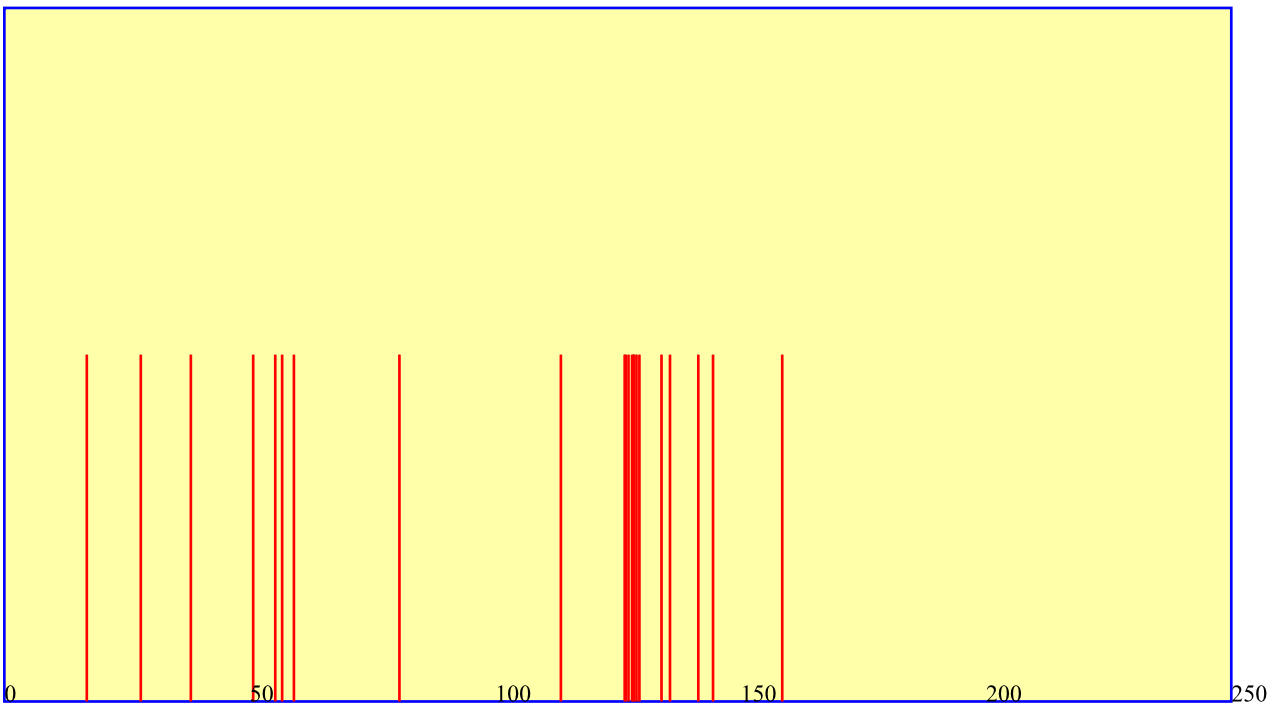
Preparation of (3S,aR)-tert-butyl 3-(3-chlorophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(14)

Preparation of (3*S*,a*R*)-*tert*-butyl 3-(3-chlorophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate14Following general procedure 2,*n*-BuLi (2.5M 2.6ml, 6.5mmol), (*R*)-*N*-a-methyl-*N*-4-methoxybenzylamine(1.61g, 6.7mmol) in THF (15ml) and (*E*)-**6**(1.12g, 3.4mmol) in THF (15ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 15:1),**14**(1.26g, 78perc) as a pale green oil
OR: [a]D= (*c*,)
IR: (film) ***()***

HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*



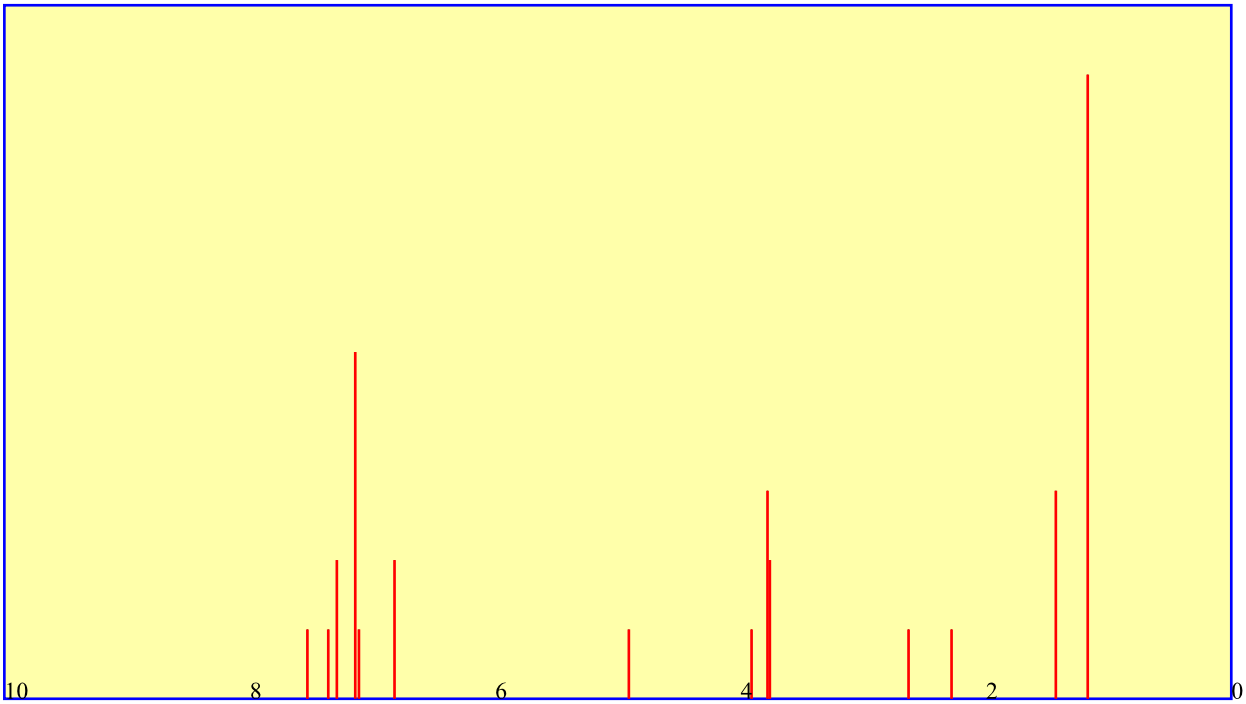
MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

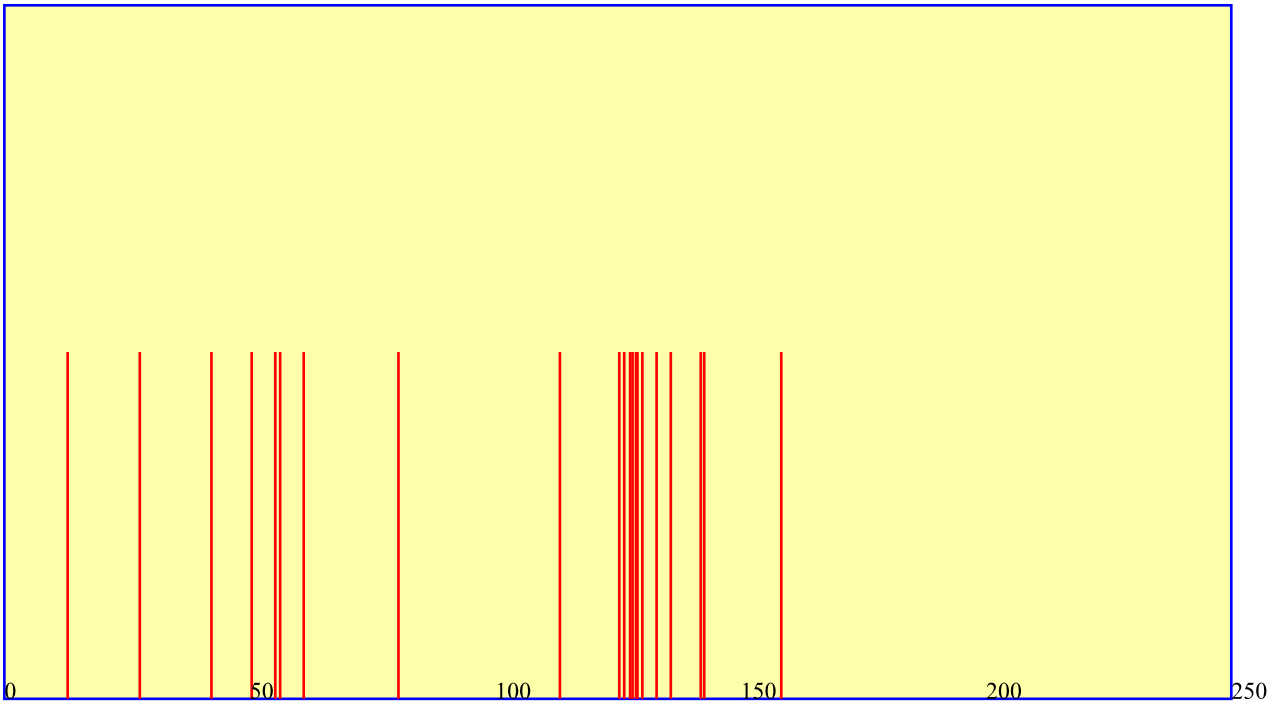
Preparation of (3S,aR)-tert-butyl 3-(2-bromophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(15)

Preparation of (3*S*,a*R*)-*tert*-butyl 3-(2-bromophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate15Following representative procedure 2,*n*-BuLi (2.5M 5.5ml, 13.7mmol), (*R*)-*N*-a-methyl-*N*-4-methoxybenzylamine(3.4g, 14.1mmol) in THF (20ml) and (*E*)-**7**(2.5g, 8.8mmol) in THF (30ml) gave, after successive purification by column chromatography on silica gel (hexane:Et [2] O 5:1) and recrystallisation,**15**as a white solid (3.77g, 82perc); Found C, 66.2; H, 7.0, N, 2.6perc; C [29] H [34] BrNO [3] requires C, 66.4; H, 6.5; N, 2.7perc; [a]+59.4 (c 1.03, CHCl [3]); v [max] (film) 1729 (C=O), 1510 (OMe), 1249 (Ph-OMe)

HNMR: 400 MHz *(CDCl [3])*



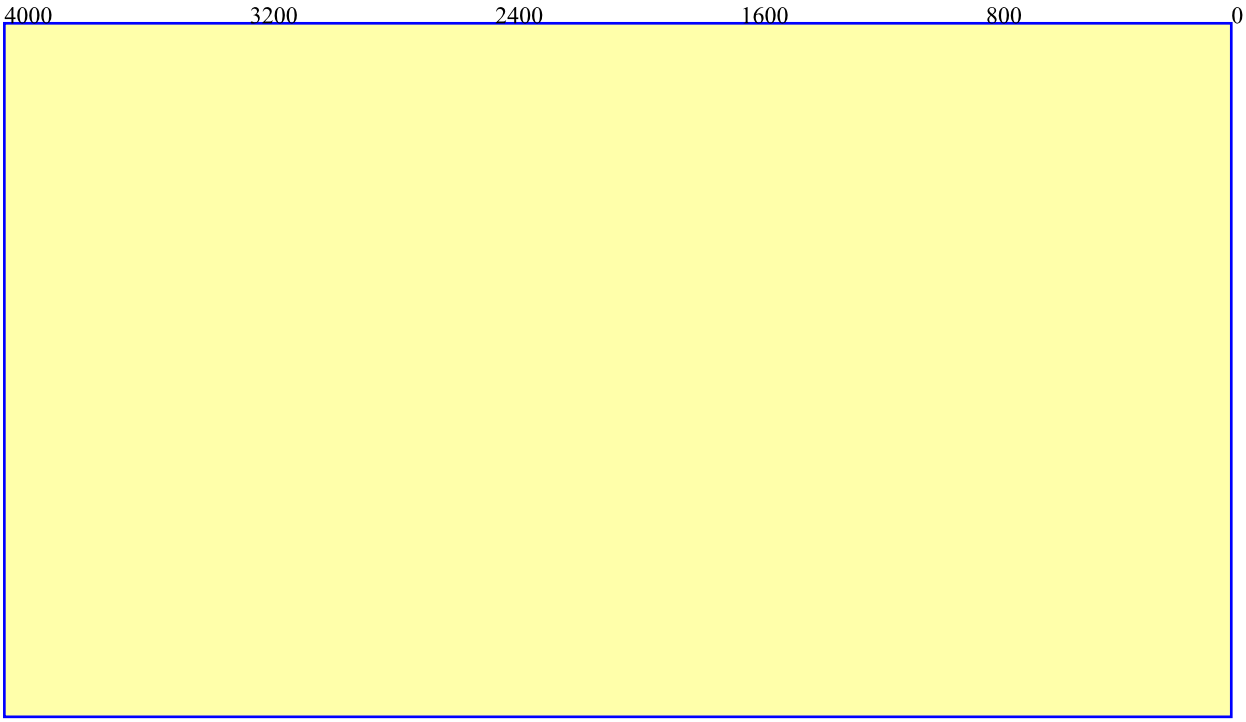
CNMR: 100 MHz *(CDCl [3])*



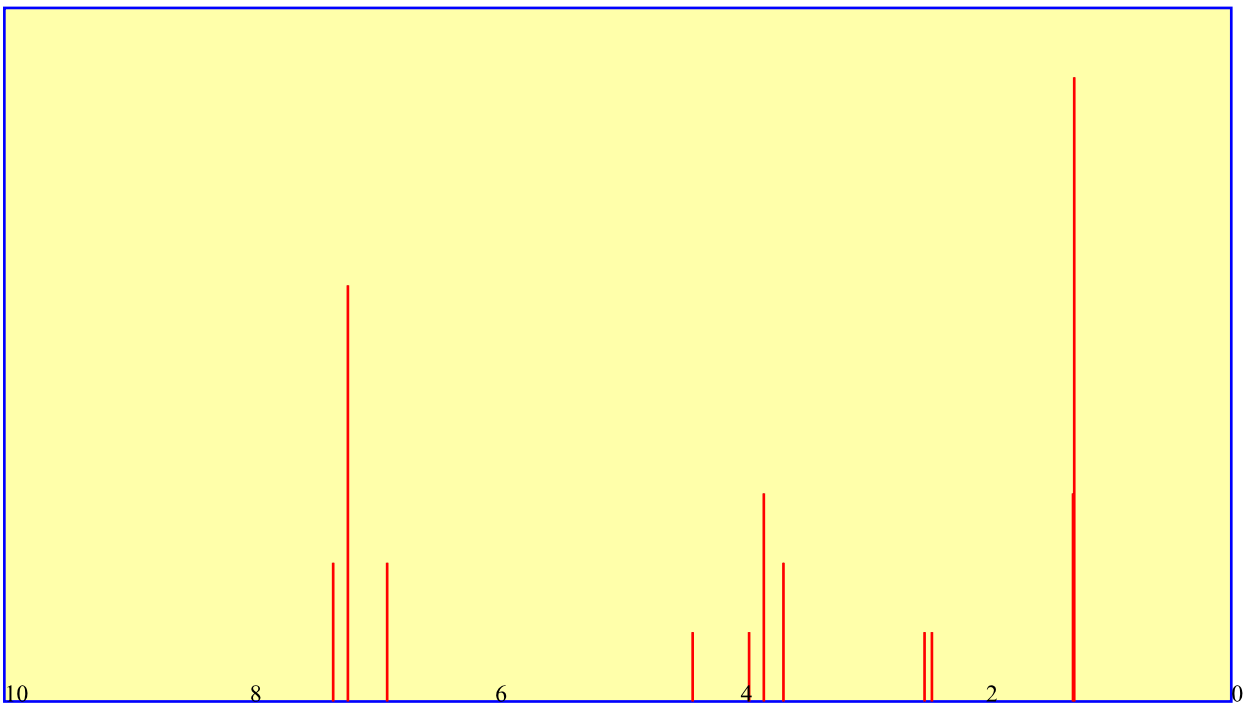
MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(3-bromophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(16)

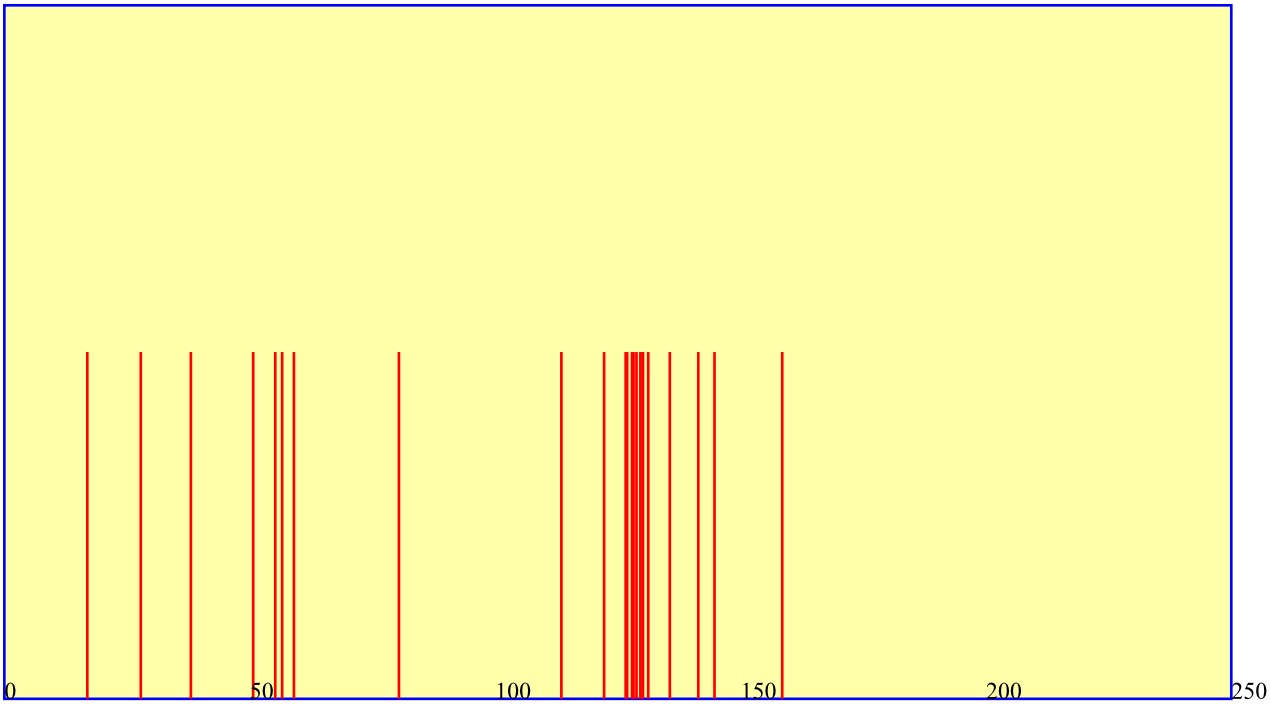
Preparation of (3*S*,a*R*)-*tert*-butyl 3-(3-bromophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate16Following general procedure 2,*n*-BuLi (2.5M 5.64ml, 14.1mmol), (*R*)-*N*-a-methyl-*N*-4-methoxybenzylamine(3.37g, 14.1mmol) in THF (20ml) and (*E*)-**8**(2.5g, 8.8mmol) in THF (30ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 5:1),**16**(3.7g, 80perc) as a colourless oil
OR: [a]D= (*c*,)
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



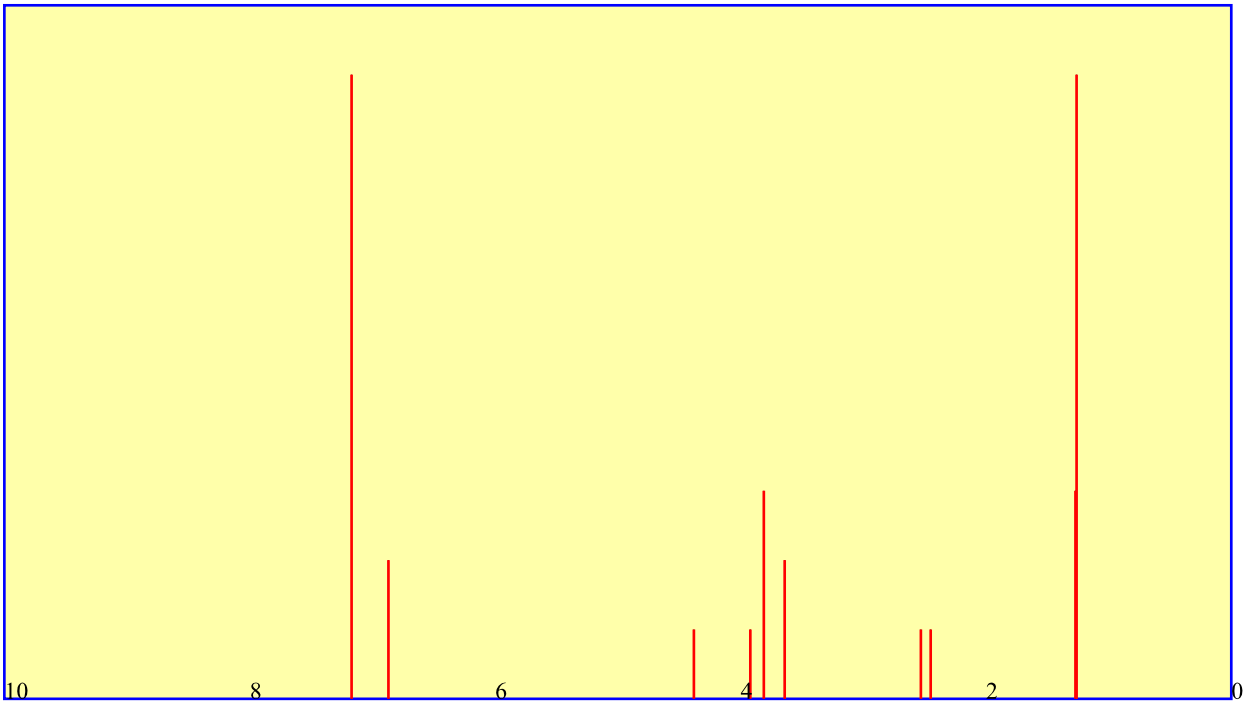
CNMR: 100 MHz *(CDCl [3])*



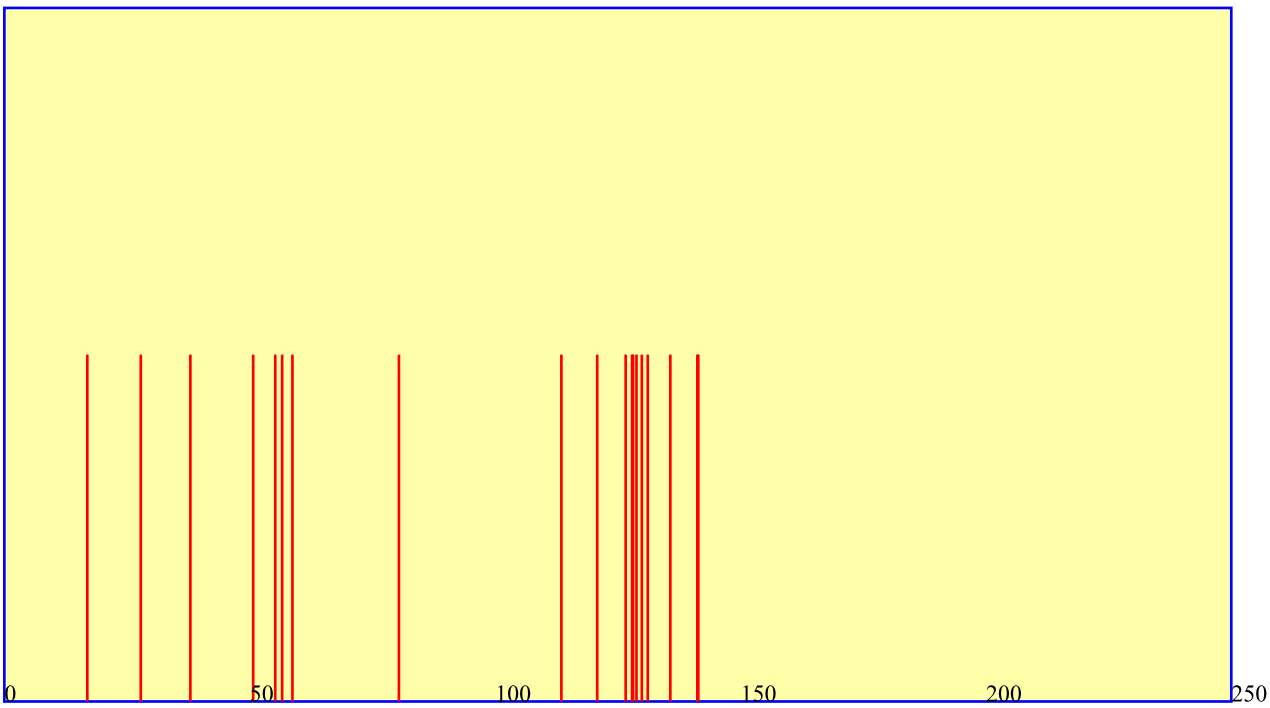
MS: APCI {+} ***()()***
Found:
Formula:
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(4-bromophenyl)-3-(N-benzyl-N-a-methyl-4-methoxybenzylamino)propanoate(17)

Preparation of (3*S*,a*R*)-*tert*-butyl 3-(4-bromophenyl)-3-(*N*-benzyl-*N*-a-methyl-4-methoxybenzylamino)propanoate17Following general procedure 2,*n*-BuLi (1.6M 3.5ml, 5.47mmol, 1.55eq), (*R*)-*N*-a-methyl-*N*-4-methoxybenzylamine(1.38g, 5.7mmol, 1.6eq) and in THF (20ml) and (*E*)-**9**(1.0g, 3.53mmol, 1.0eq) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 6:1)**17**(1.60g, 86perc) as a colourless oil
OR: [a]D= (*c*,)
HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

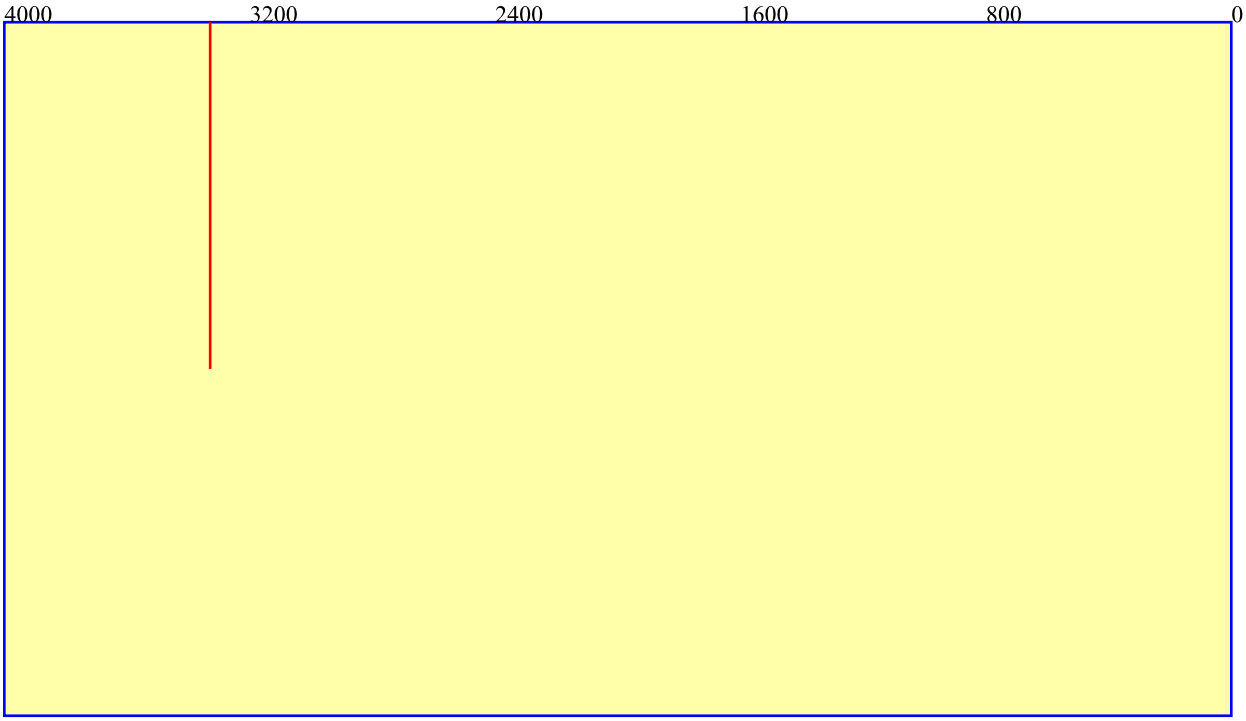


MS: APCI {+} *()()*
Found:
Formula:

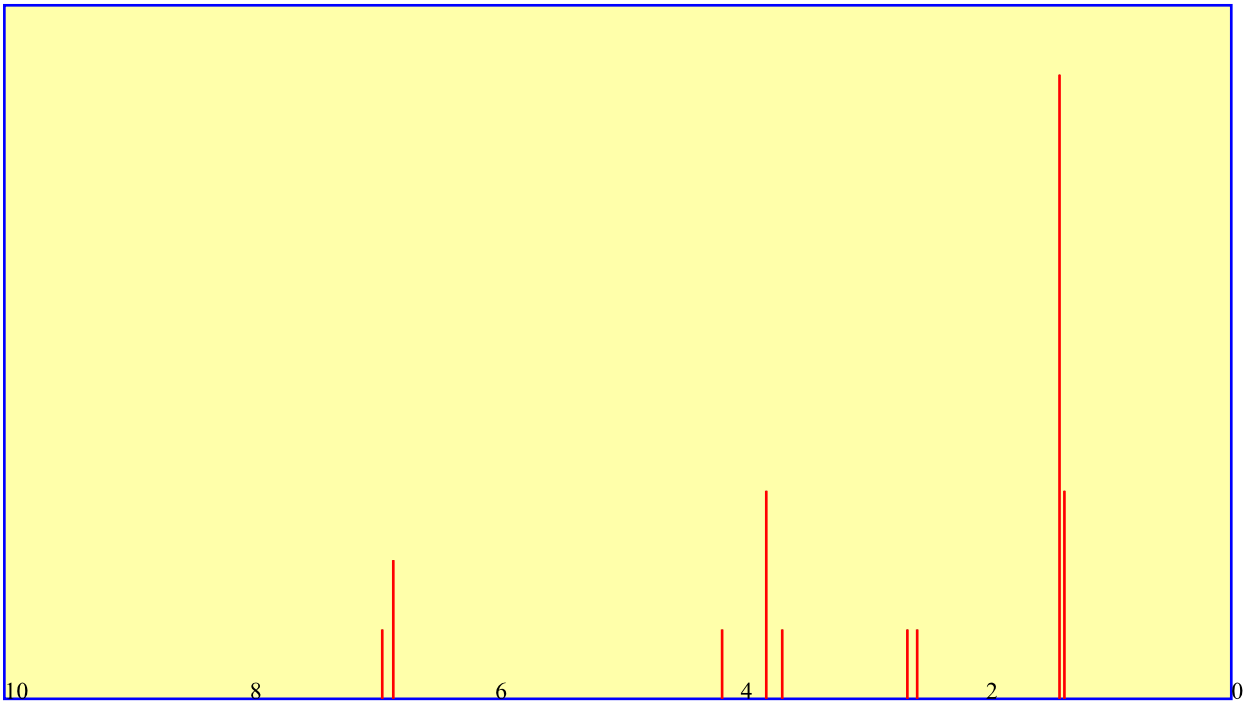
method:
Required:
overall:

Preparation of (3R,aS)-tert-butyl 3-(3-fluorophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(18)

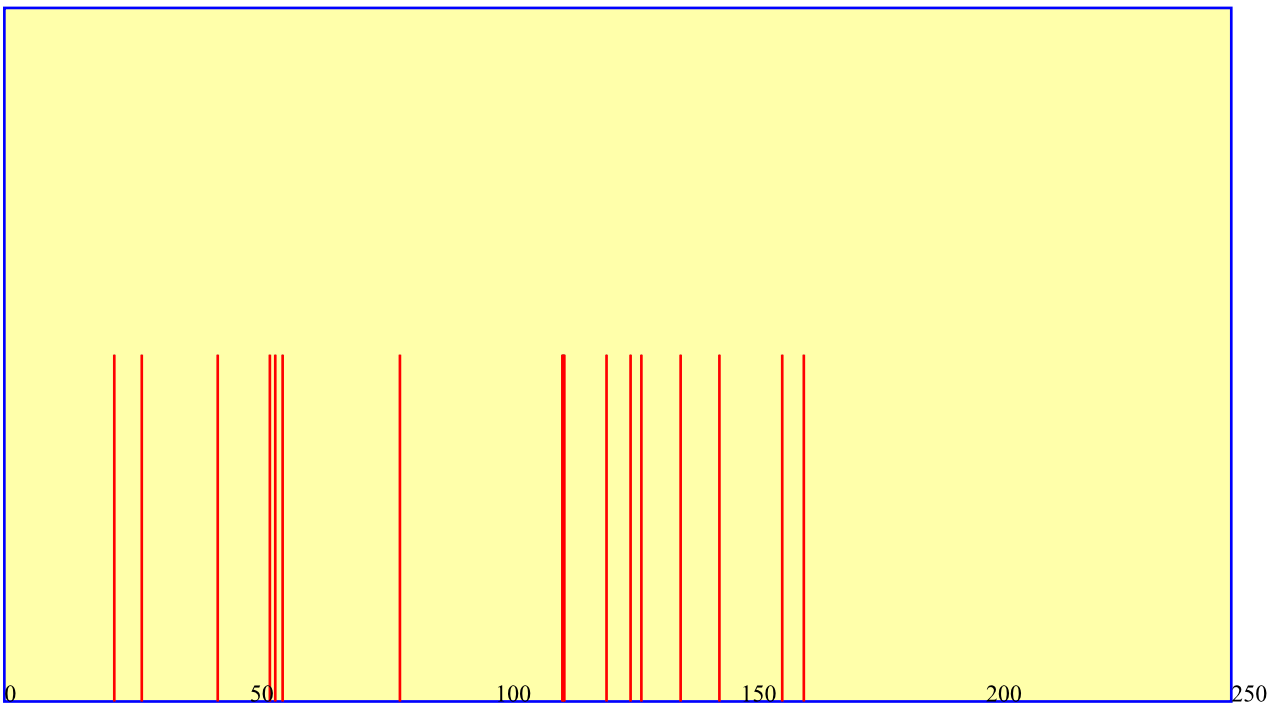
Preparation of (3*R*,a*S*)-*tert*-butyl 3-(3-fluorophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate18Following general procedure 3, CAN (2.49g, 4.53mmol) and**10**(1.0g, 2.16mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work and purification by column chromatography on silica gel (hexane:Et [2] O 4:1:1perc NEt [3]),**18**(706mg, 86perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) ***(cm {-1})***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*



MS: APCI {+} *()()*
Found:
Formula:

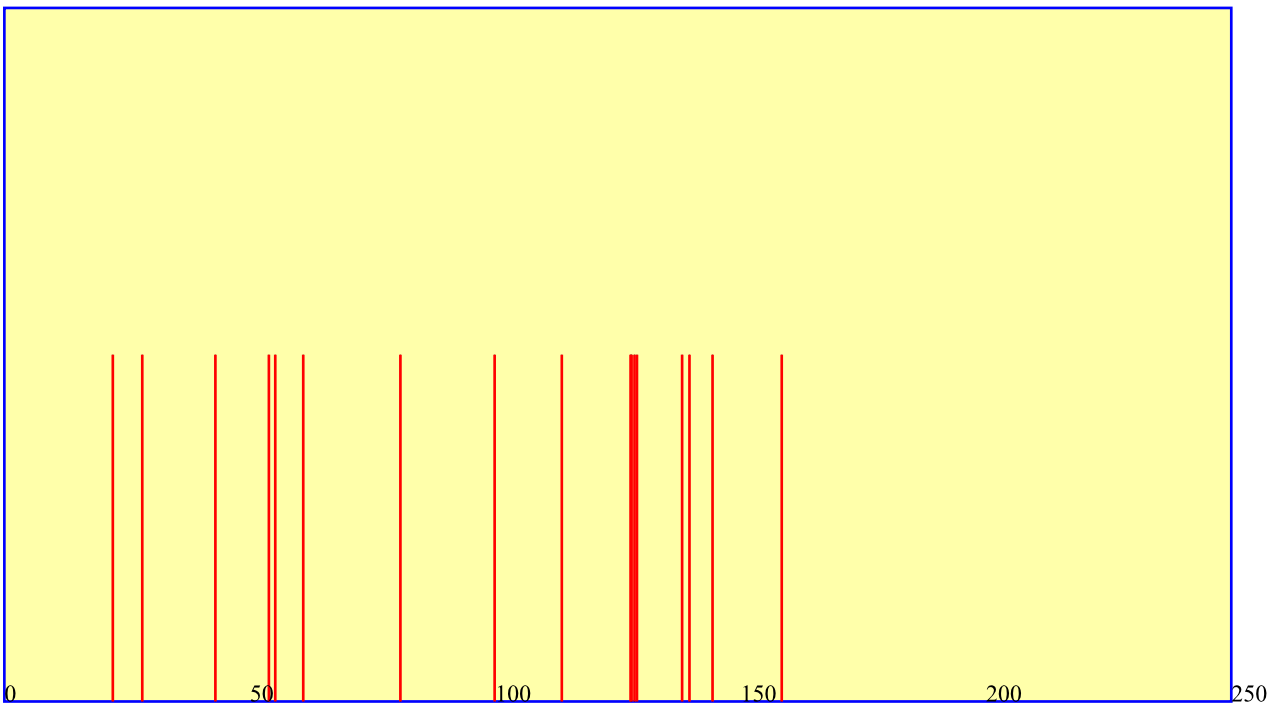
method:
Required:
overall:

Preparation of (3R,aS)-tert-butyl 3-(2-iodophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(19)

Preparation of (3*R*,a*S*)-*tert*-butyl 3-(2-iodophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate19Following general procedure 3, CAN (7.05g, 12.8mmol) and**11**(3.5g, 6.12mmol) in 5:1 MeCN:H [2] O (90ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**19**(632mg, 75perc) as a pale green oil
IR: (film) ***()***

OR: [a]D= (*c*,)
HNMR: 400 MHz ***(CDCl [3])***

CNMR: 100 MHz *(CDCl [3])*

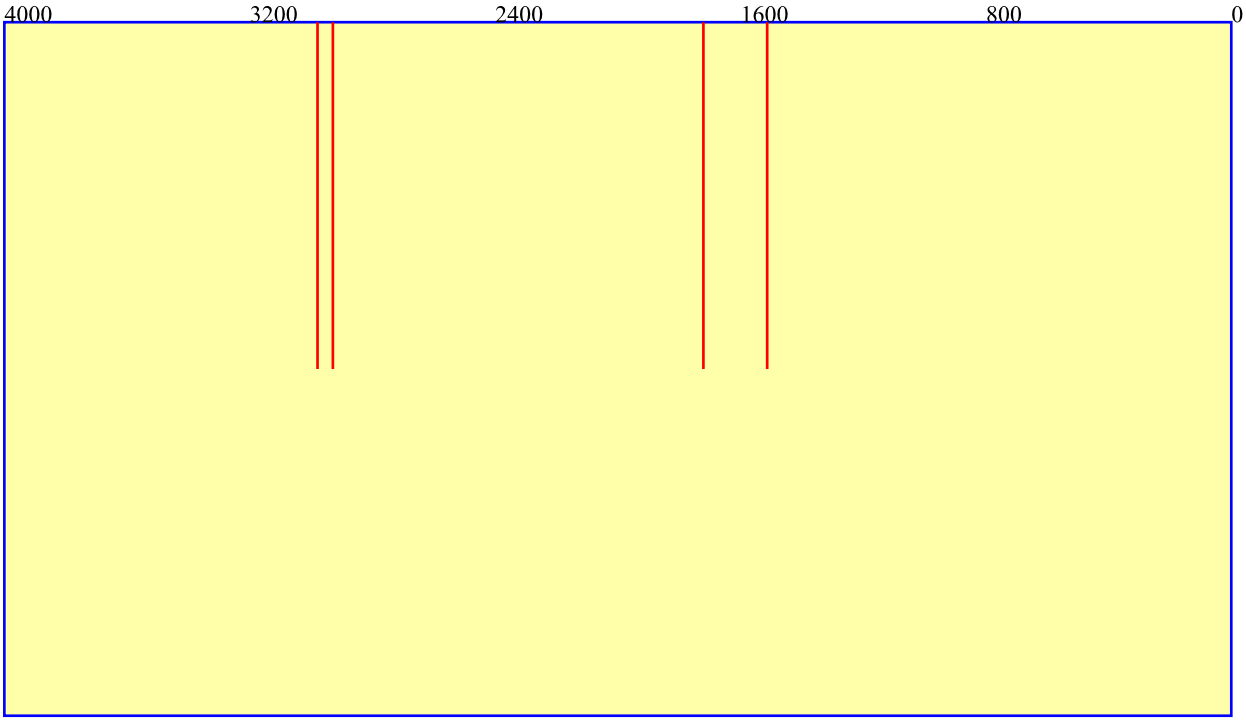


MS: CI {+} *()()*
Found:
Formula:

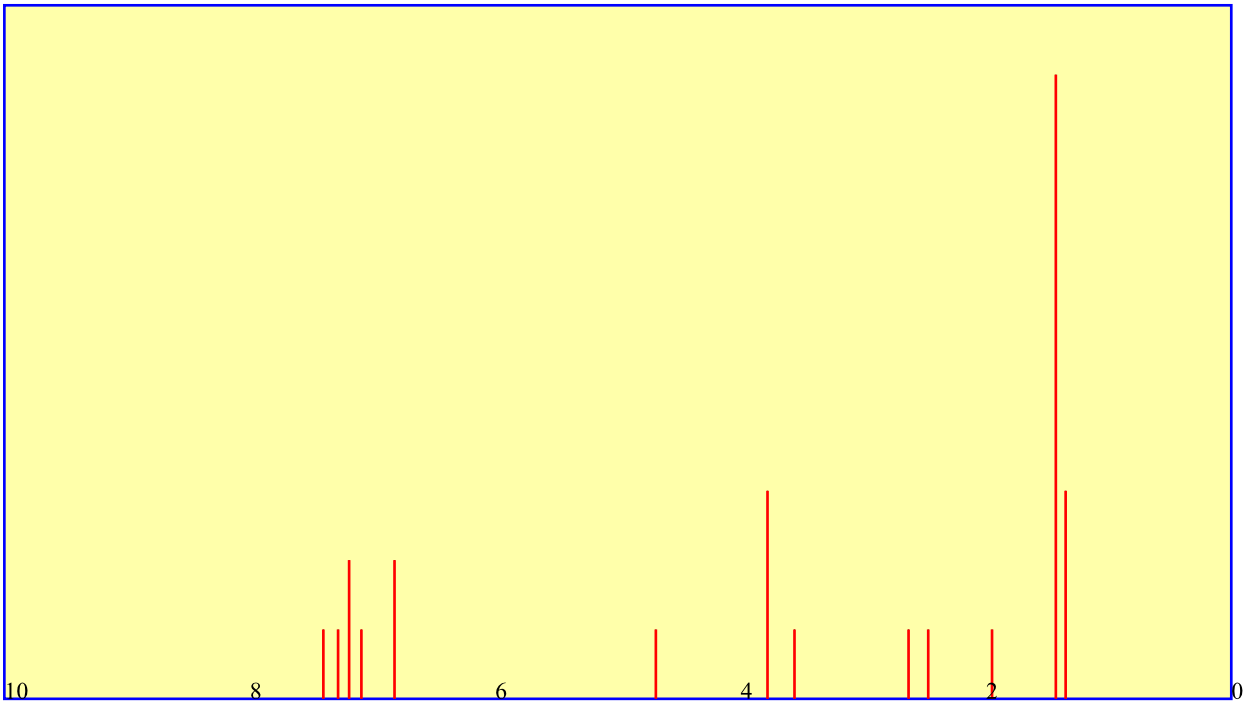
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(2-bromophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(20)

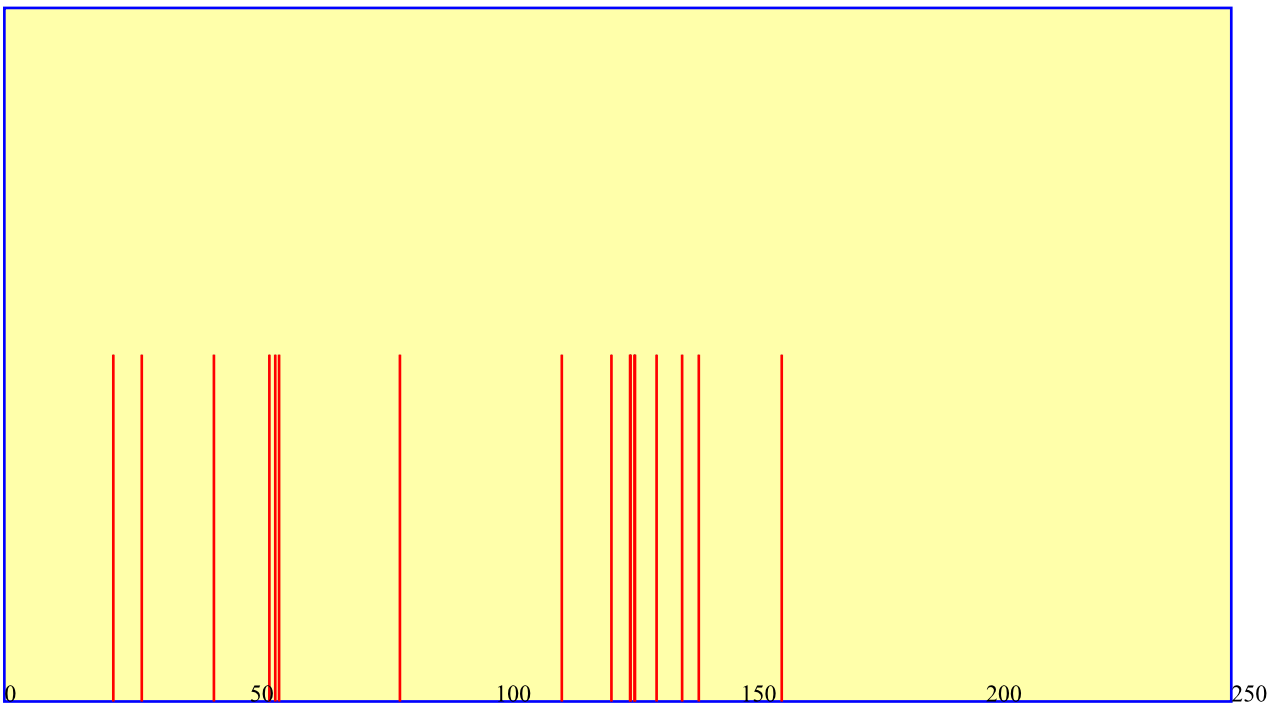
Preparation of (3*S*,a*R*)-*tert*-butyl 3-(2-bromophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate20Following general procedure 3, CAN (6.59g, 12.0mmol) and**15**(3.0g, 5.73mmol) in 5:1 MeCN:H [2] O (60ml) gave, after work up and purification by column chromatography on silica gel (hexane:EtOAc 9:1:1perc NEt [3]),**19**(2.14g, 86perc) as a colourless oil
IR: (film) *()*



OR: [a]D= (*c*,)
HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

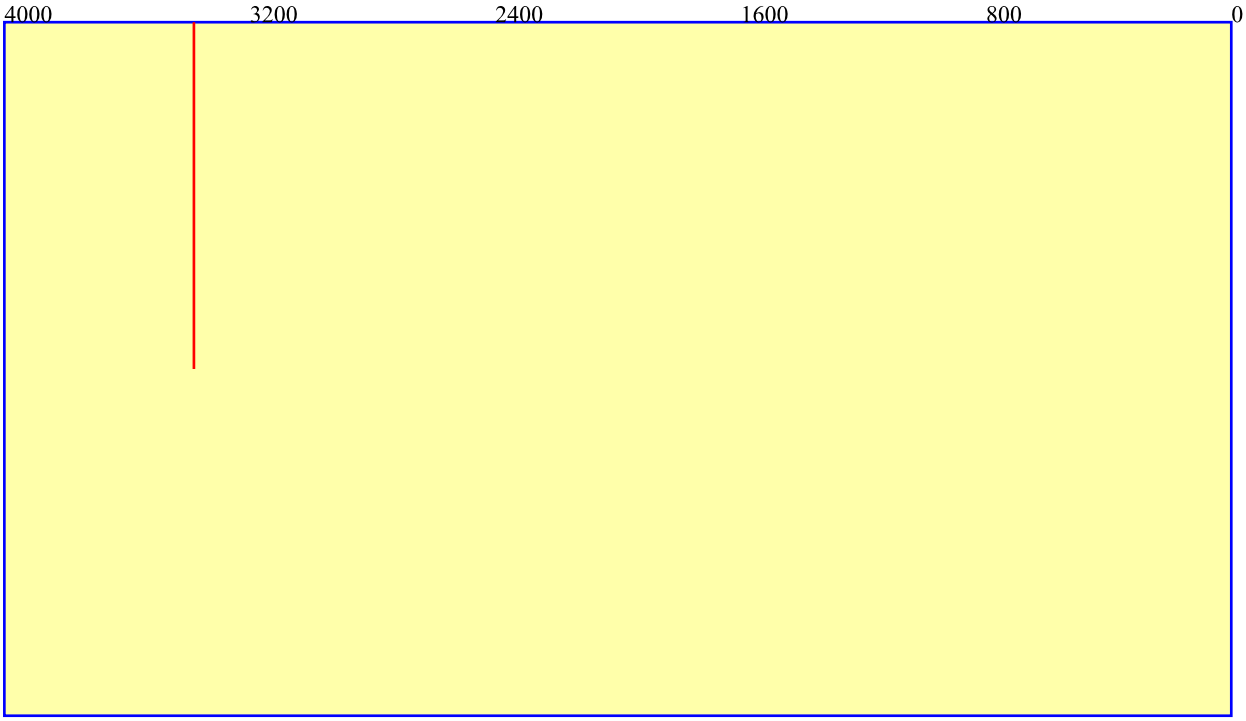


MS: APCI {+} *()()*
Found:
Formula:

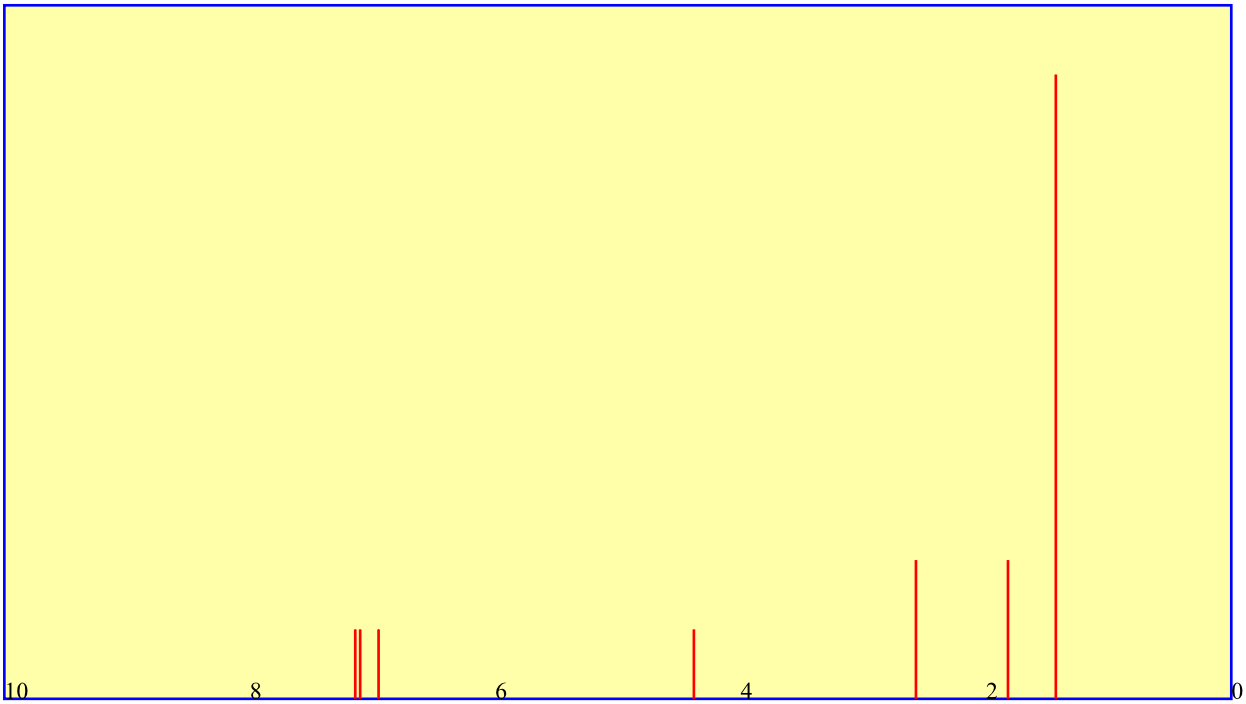
method:
Required:
overall:

Preparation of (R)-tert-butyl 3-(3-fluorophenyl)-3-aminopropanoate(21)

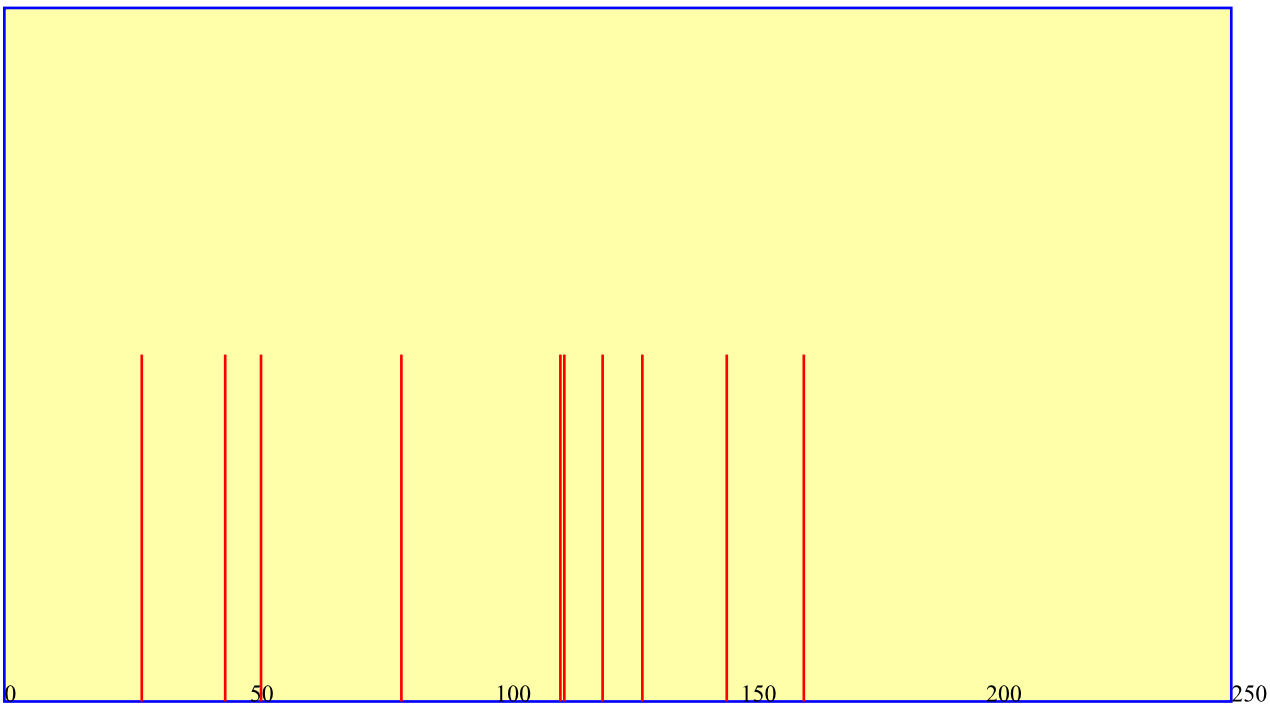
Preparation of (*R*)-*tert*-butyl 3-(3-fluorophenyl)-3-aminopropanoate21Following general procedure 4, CAN (2.19g, 4.0mmol) and 18 (373mg, 1.0mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:1), 21 (126mg, 53perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

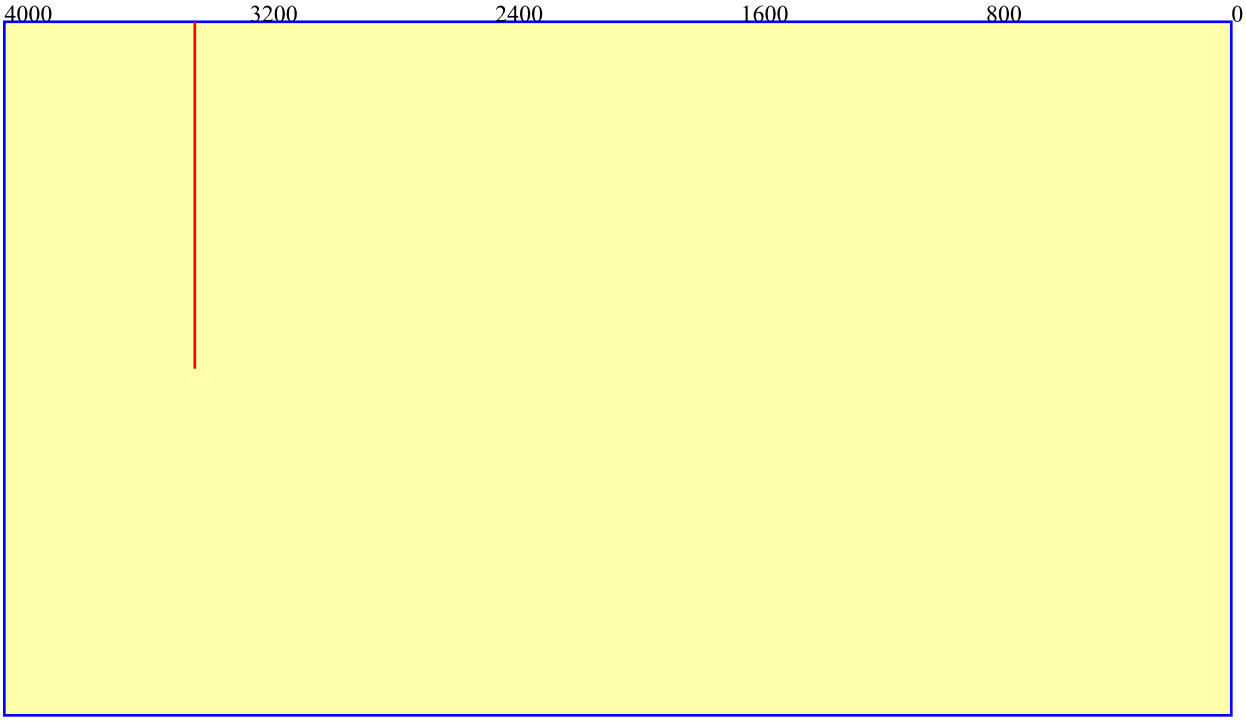


MS: APCI {+} *()()*
Found:
Formula:

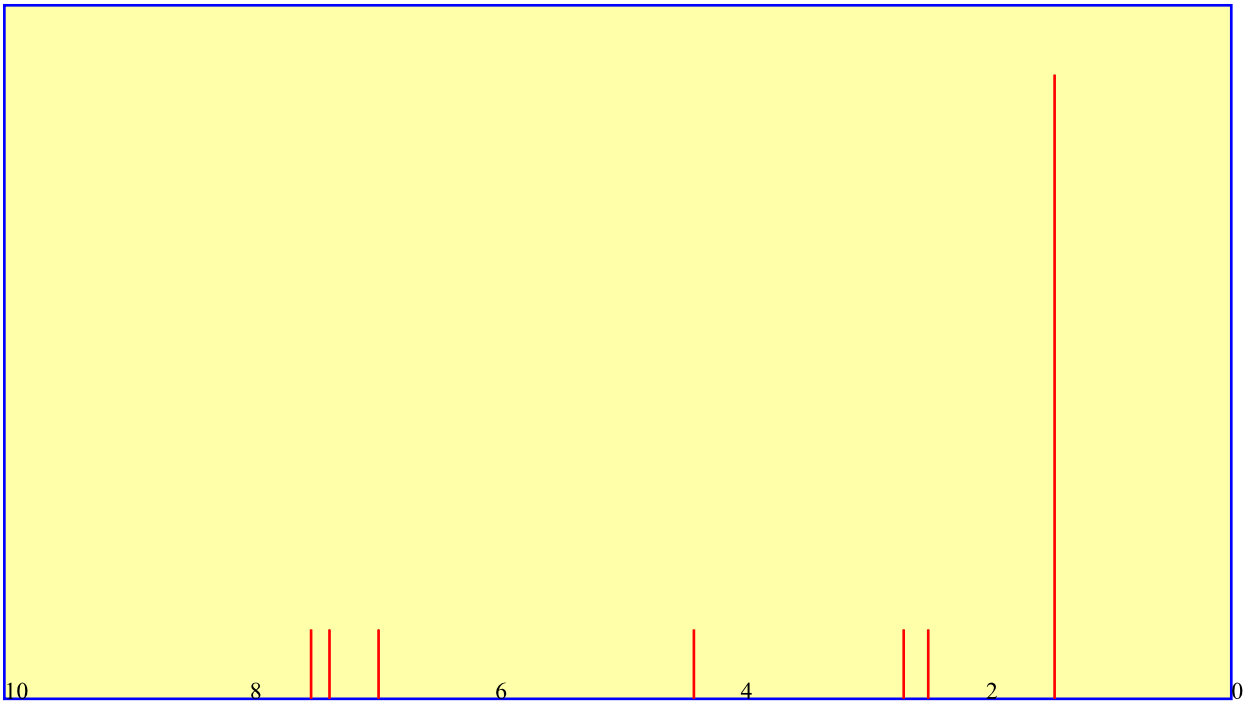
method:
Required:
overall:

Preparation of (R)-tert-butyl 3-(2-iodophenyl)-3-aminopropanoate(22)

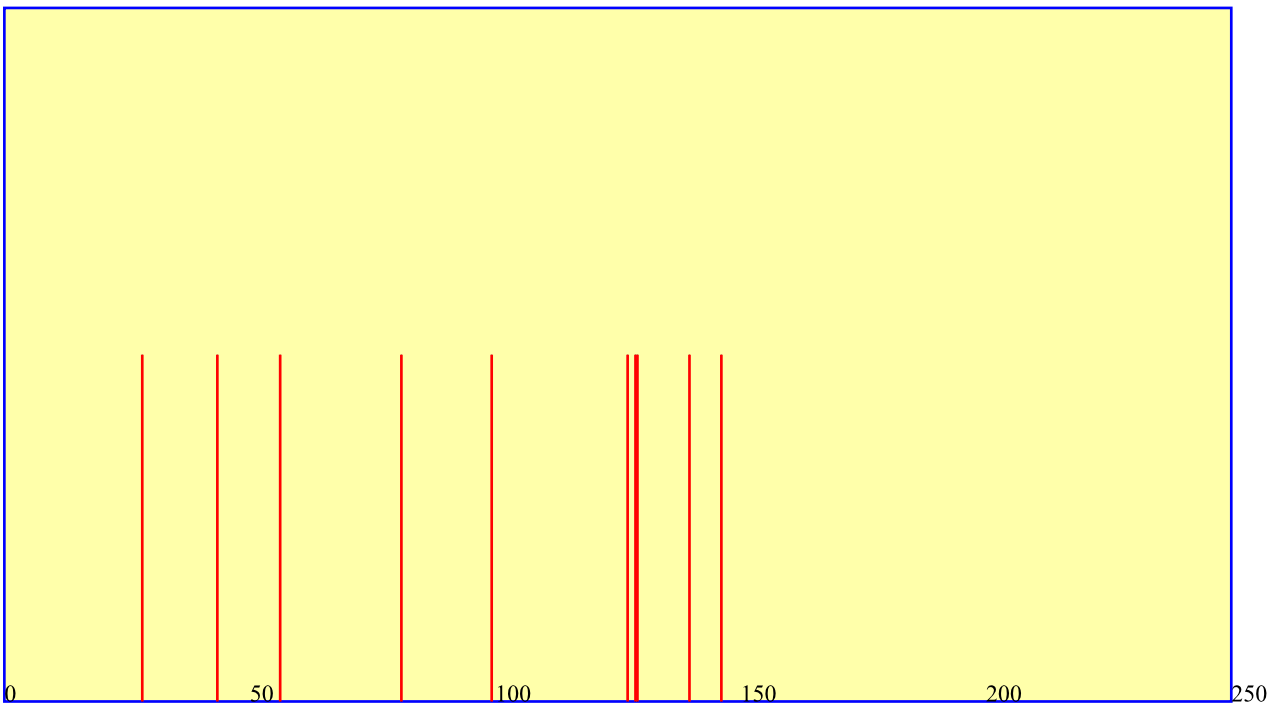
Preparation of (*R*)-*tert*-butyl 3-(2-iodophenyl)-3-aminopropanoate22Following general procedure 4, CAN (4.56g, 8.31mmol) and**19**(1.0g, 2.08mmol) in 5:1 MeCN:H [2] O (24ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**22**(368mg, 51perc) as a pale green oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*



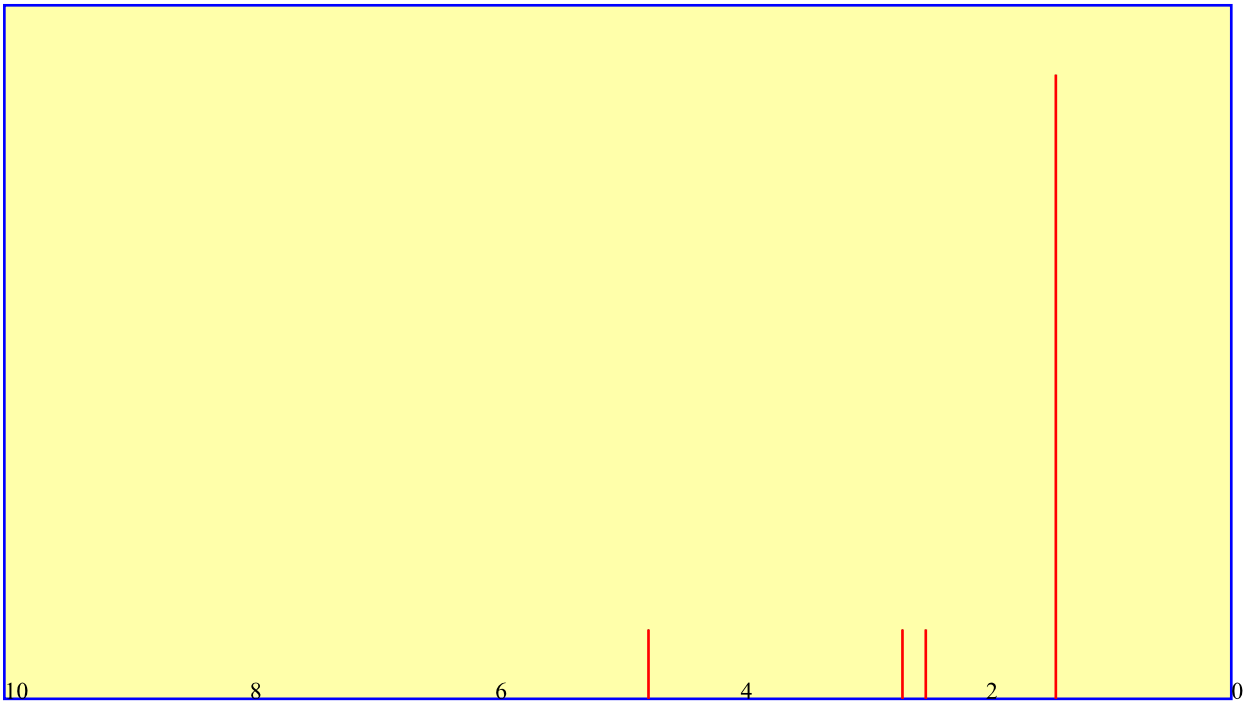
MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

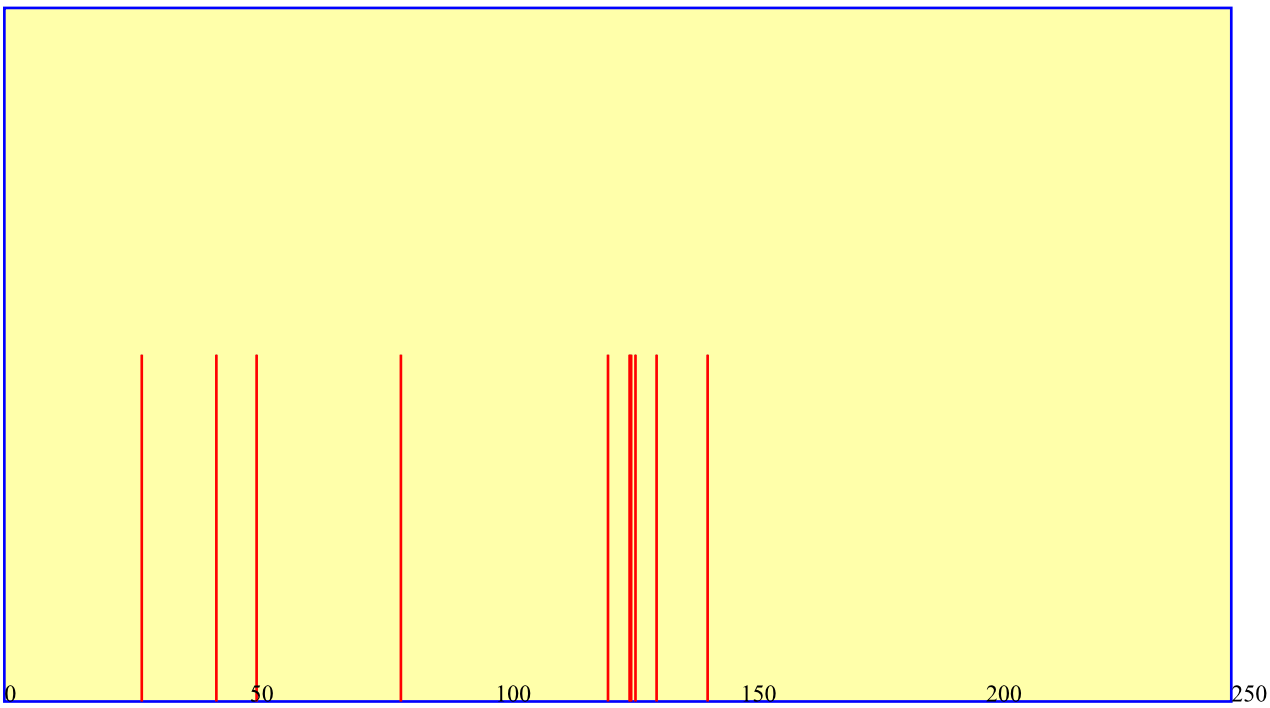
Preparation of (S)-tert-butyl 3-(2-bromophenyl)-3-aminopropanoate(23)

Preparation of (*S*)-*tert*-butyl 3-(2-bromophenyl)-3-aminopropanoate23Following general procedure 4, CAN (2.71g, 4.94mmol) and**20**(536mg, 1.24mmol) in 5:1 MeCN:H [2] O (24ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:1),**23**(254mg, 68perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) ***()***

HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

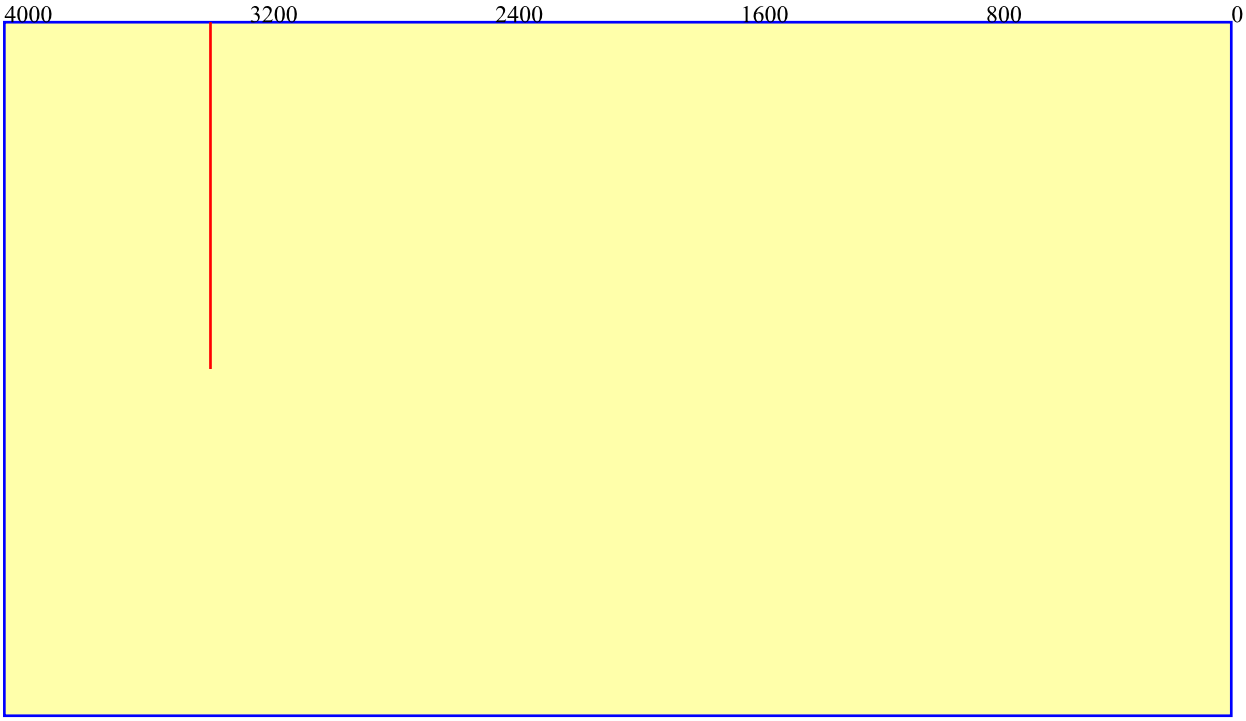


MS: APCI {+} *()()*
Found:
Formula:

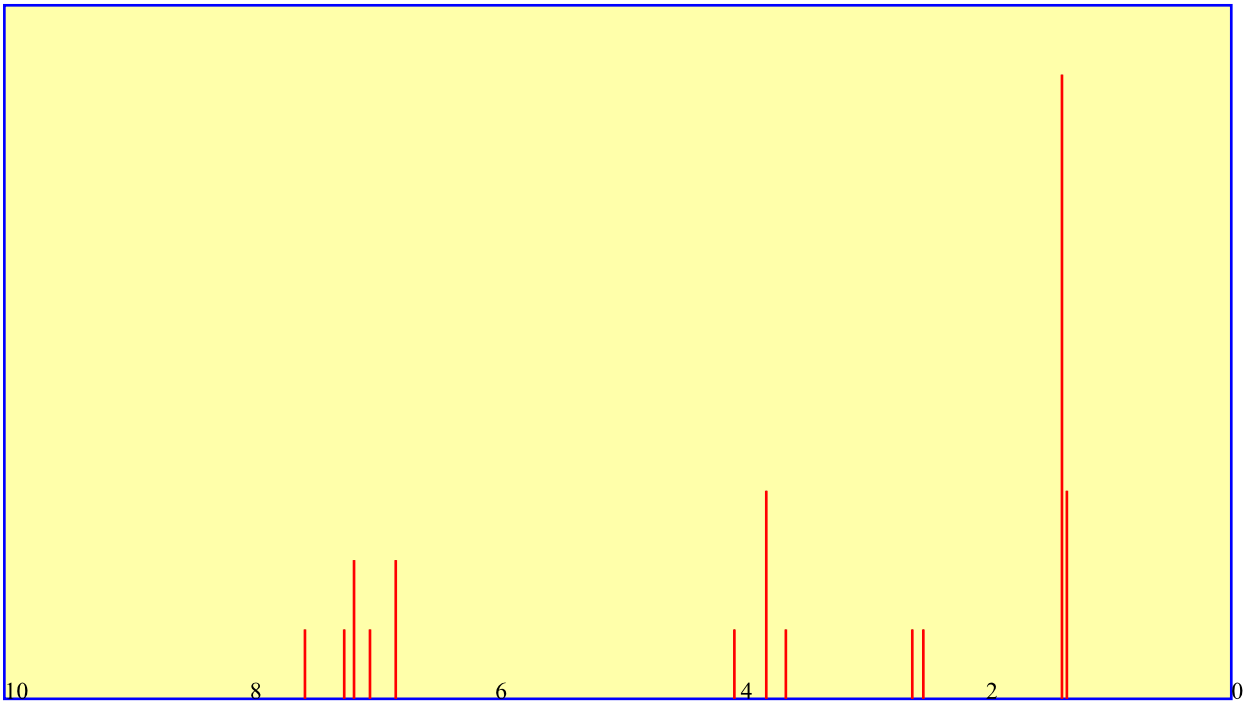
method:
Required:
overall:

Preparation of (3R,aS)-tert-butyl 3-(3-iodophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(24)

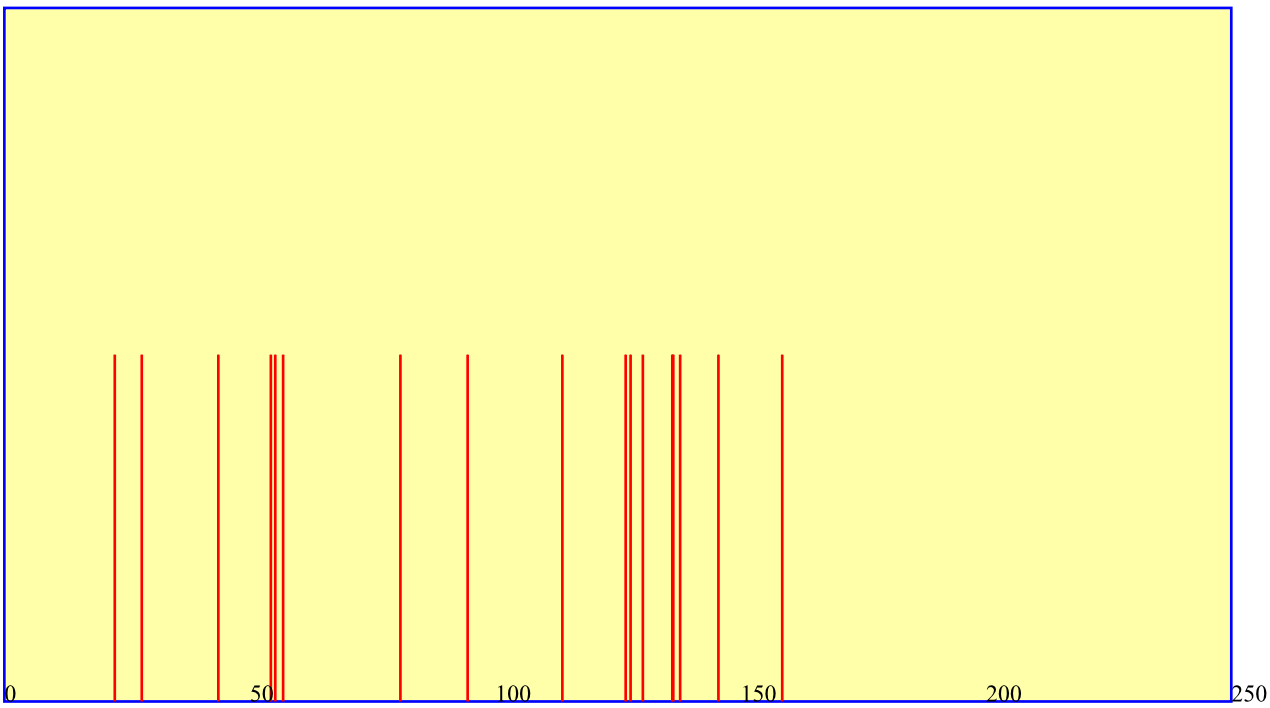
Preparation of (3*R*,a*S*)-*tert*-butyl 3-(3-iodophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate24Following general procedure 3, CAN (2.01g, 3.7mmol) and**12**(2.0g, 3.5mmol) in 5:1 MeCN:H [2] O (24ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**24**(1.30g, 77perc) as a pale green oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

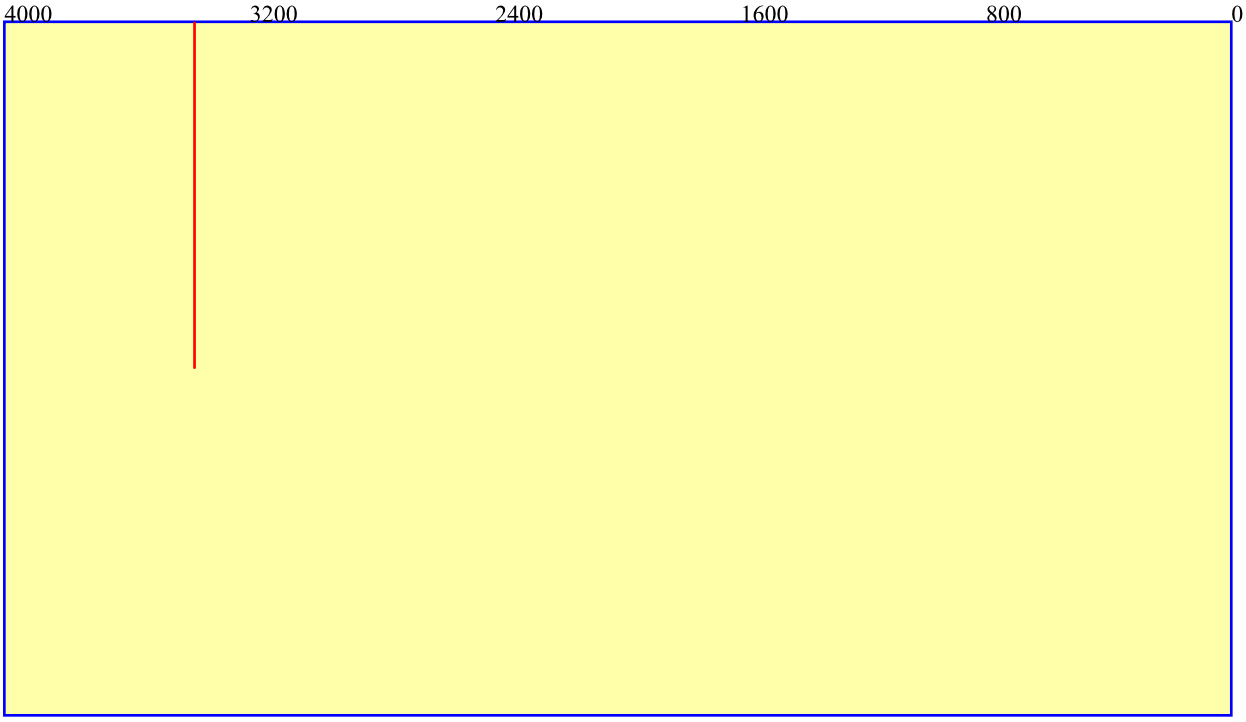


MS: APCI {+} *()()*
Found:
Formula:

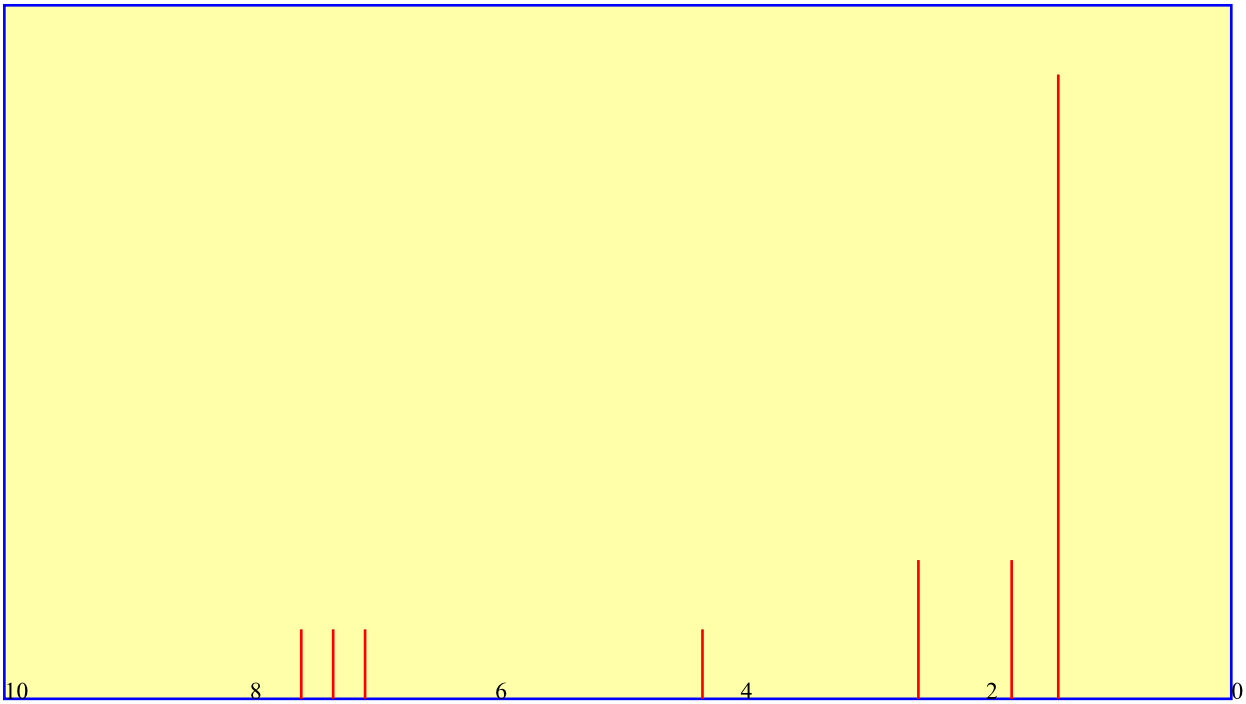
method:
Required:
overall:

Preparation of (R)-tert-butyl 3-(3-iodophenyl)-3-aminopropanoate(25)

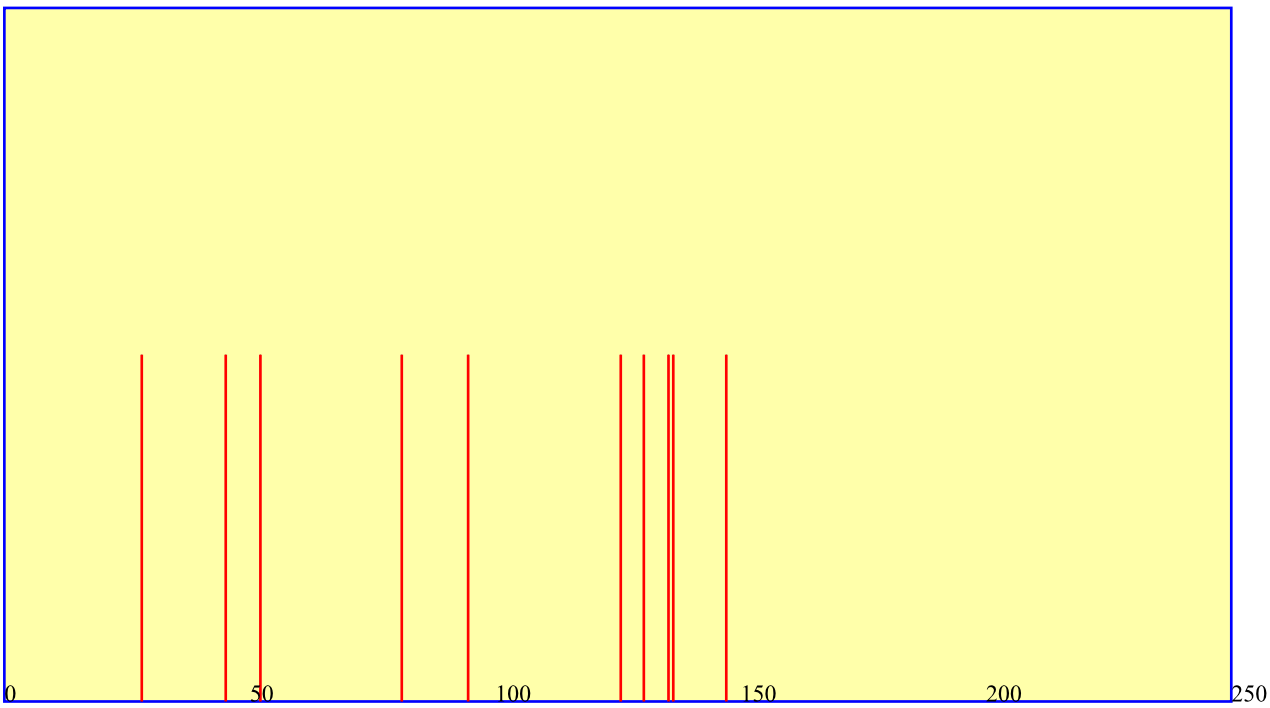
Preparation of (*R*)-*tert*-butyl 3-(3-iodophenyl)-3-aminopropanoate25Following general procedure 4, CAN (3.10g, 5.65mmol) and**24**(680mg, 1.41mmol) in 5:1 MeCN:H [2] O (18ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:2),**25**(240mg, 49perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

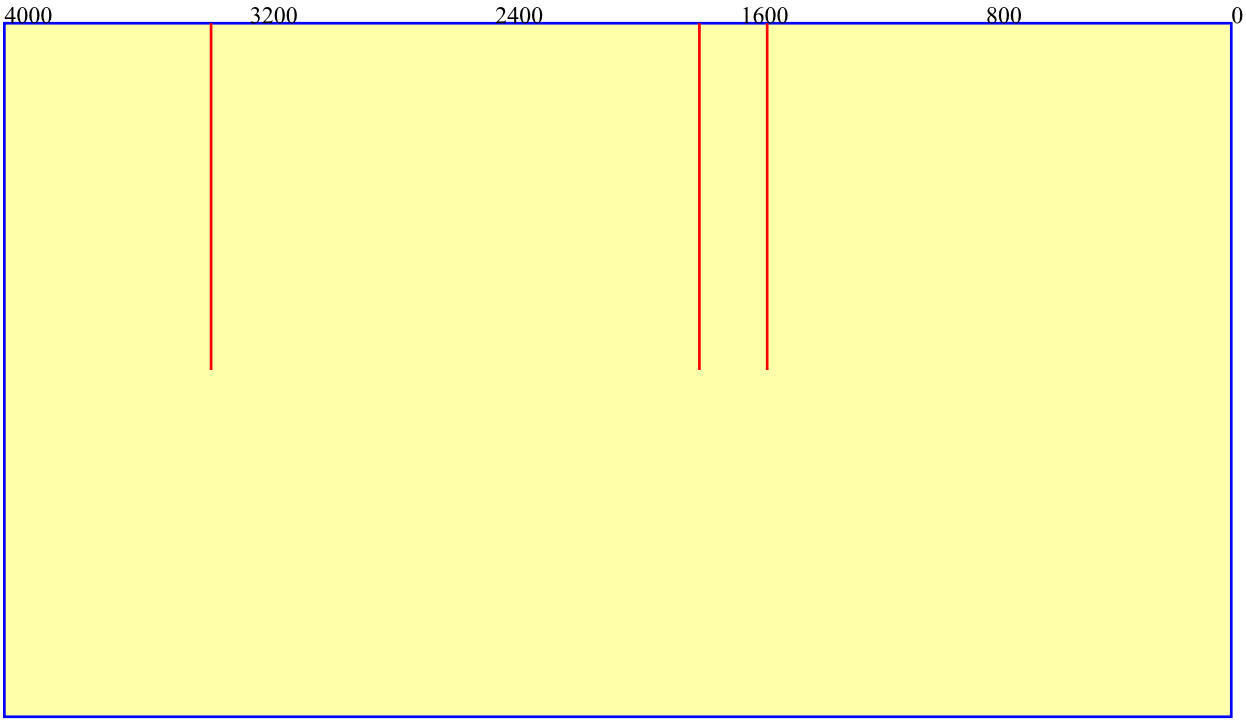


MS: APCI {+} *()()*
Found:
Formula:

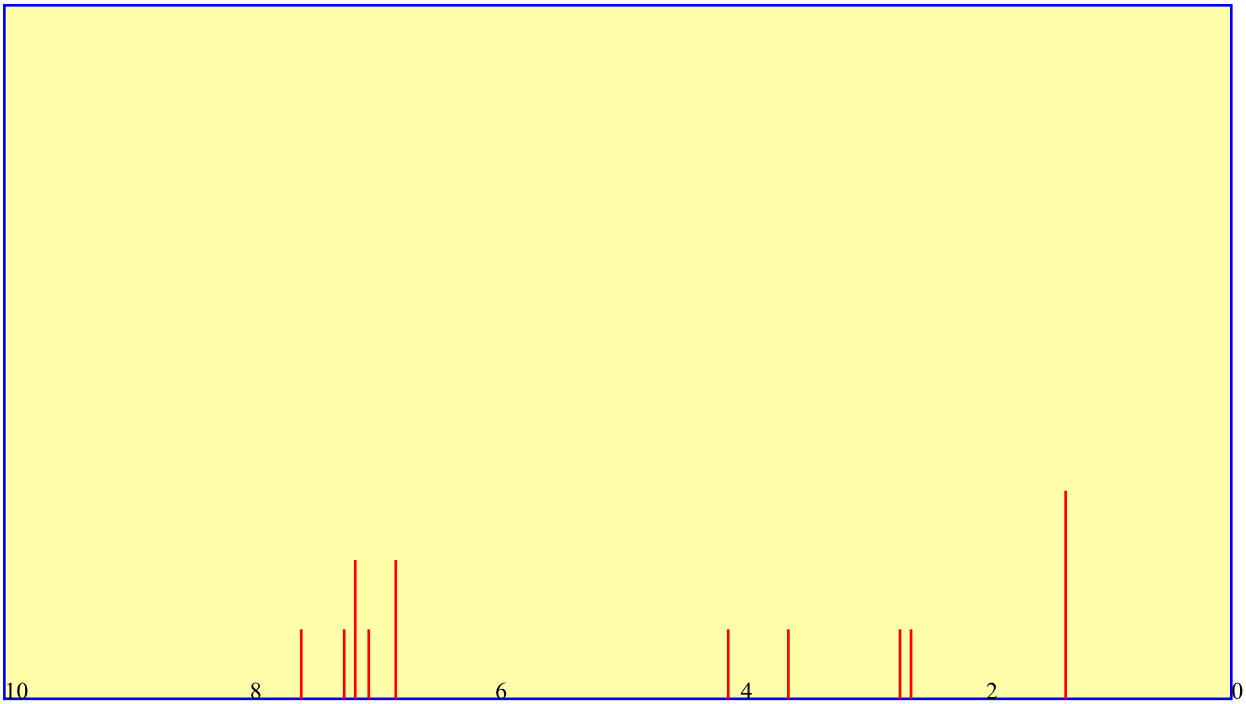
method:
Required:
overall:

Preparation of (3R,aS)-methyl 3-(3-iodophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(26)

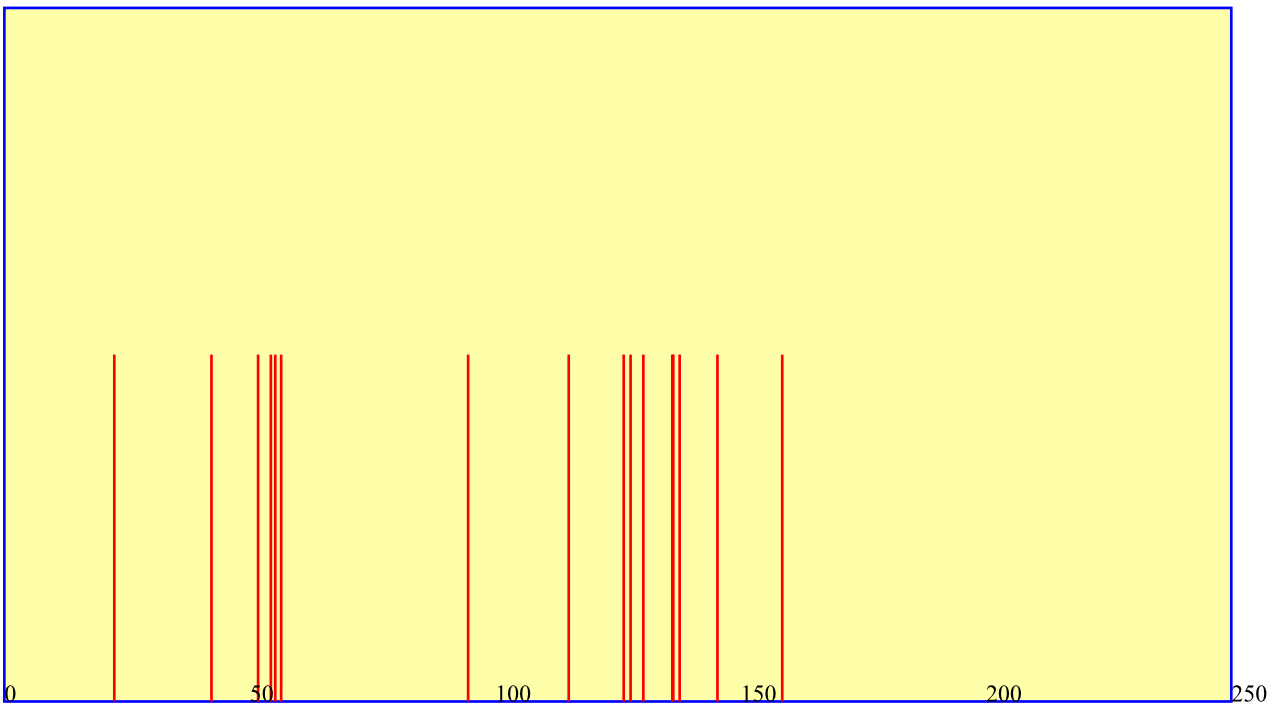
Preparation of (3*R*,a*S*)-methyl 3-(3-iodophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate26Following general procedure 5,**24**(1.5g, 3.12mmol) was added to a saturated solution of HCl in MeOH (20ml). After concentration*in vacuo*, recrystallisation (EtOAc:hexane) and treated with saturated aqueous NaHCO [3] gave**26**(1.03g, 75perc) as a colourless oil; mp (HCl salt) 168-169C (EtOAc:hexane); Found: C, 48.0; H, 4.8; N, 3.0perc; C [19] H [23] IClNO [3] requires C, 48.0; H, 4.9; N, 2.9perc
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*



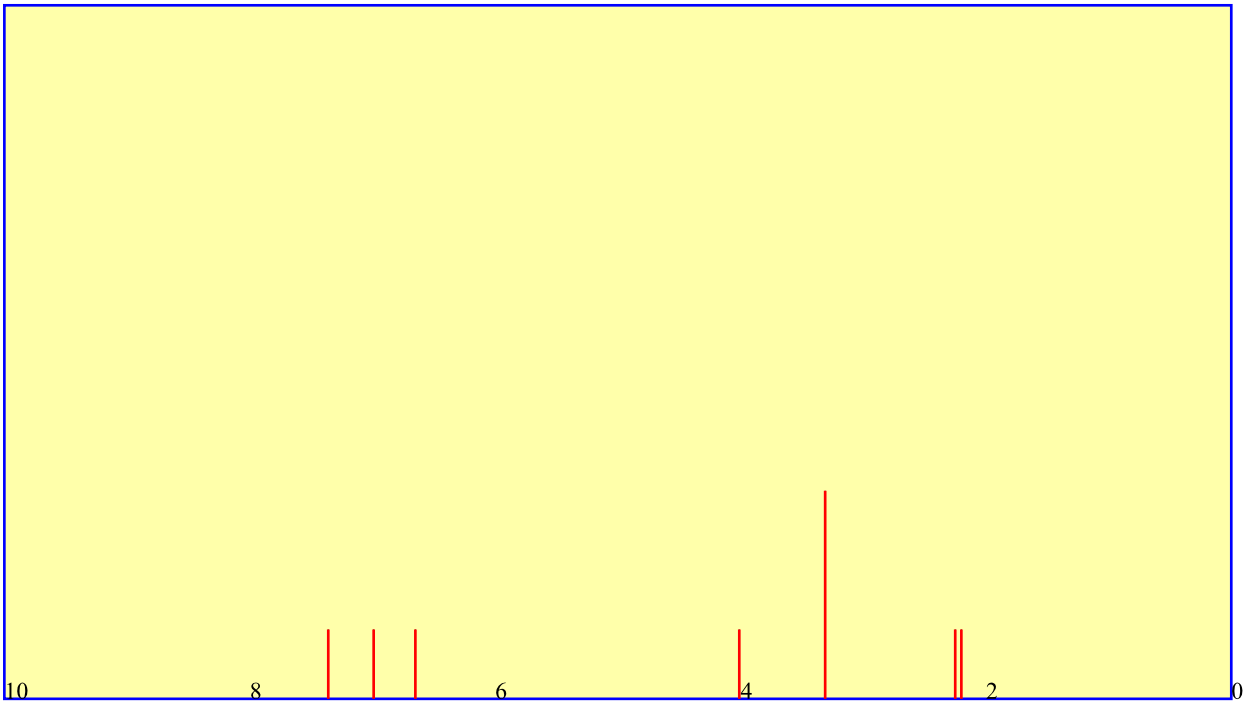
MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

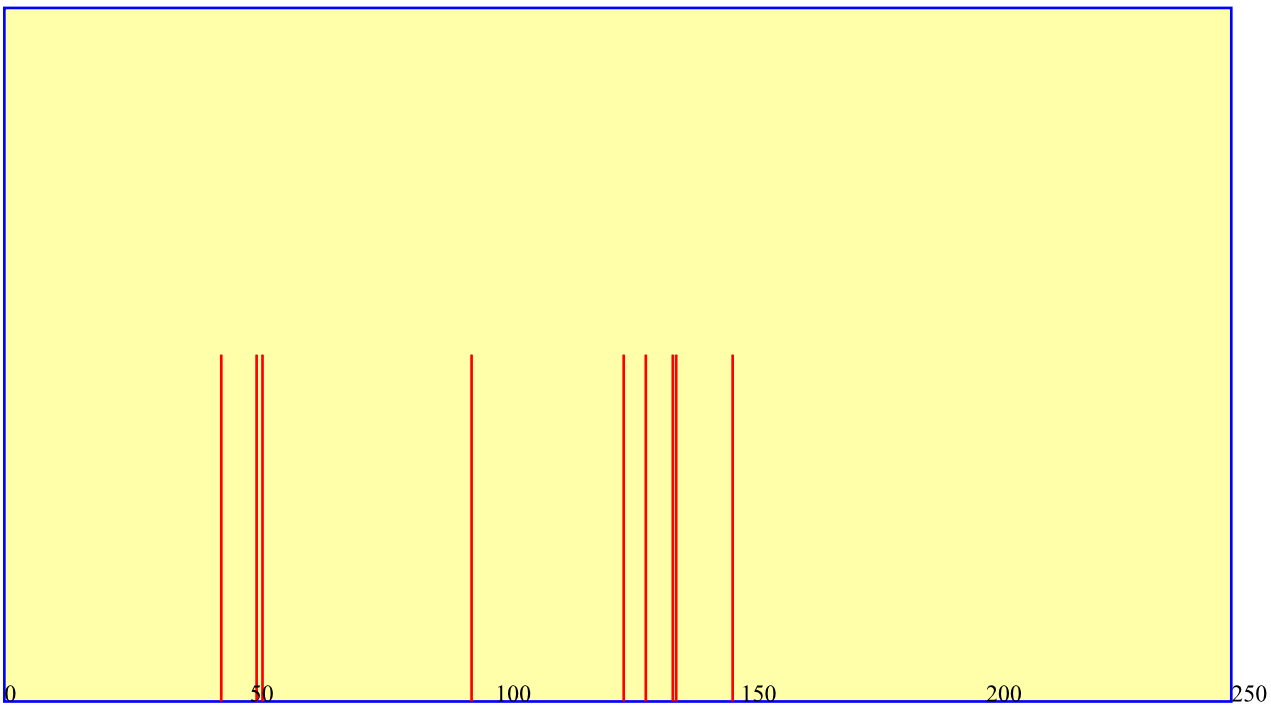
Preparation of (R)-methyl 3-(3-iodophenyl)-3-aminopropanoate(27)

Preparation of (*R*)-methyl 3-(3-iodophenyl)-3-aminopropanoate27Following general procedure 4, CAN (1.90g, 3.46mmol) and**26**(380mg, 0.85mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:2:1perc NEt [3]), gave**27**(125mg, 48perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) ***()***

HNMR: 400 MHz ***(toluene-d [8])***



CNMR: 100 MHz *(toluene-d [8])*



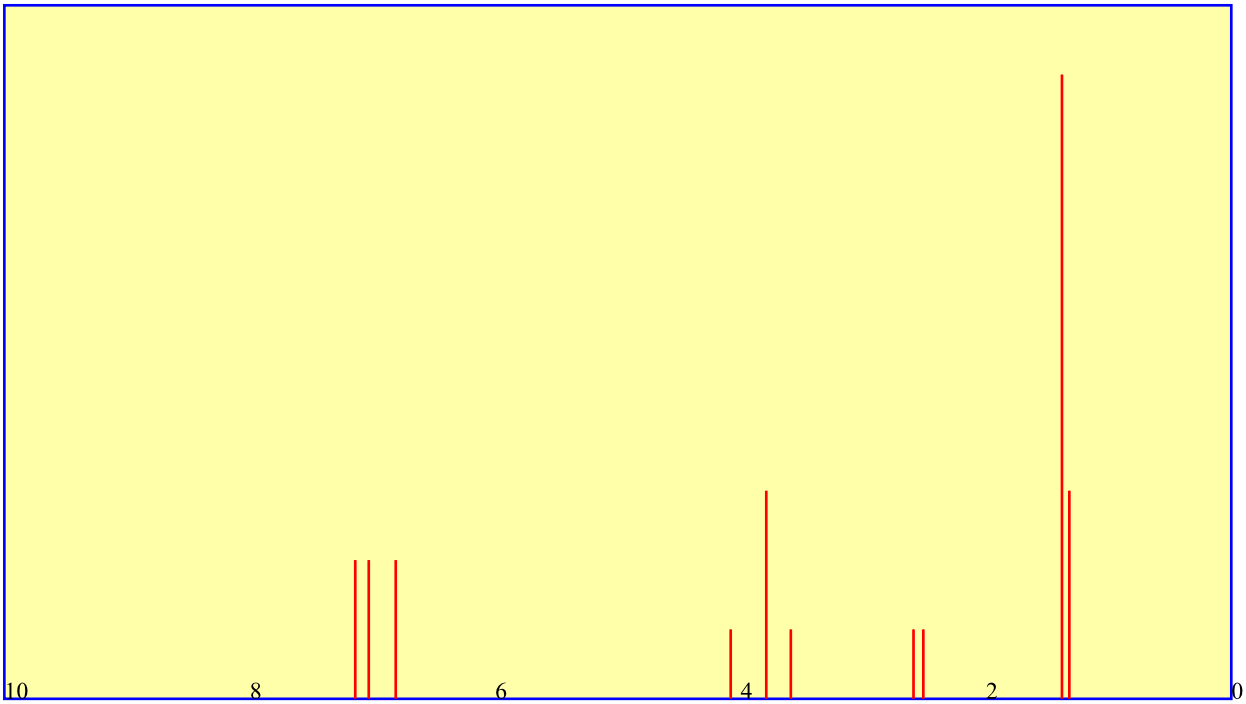
MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

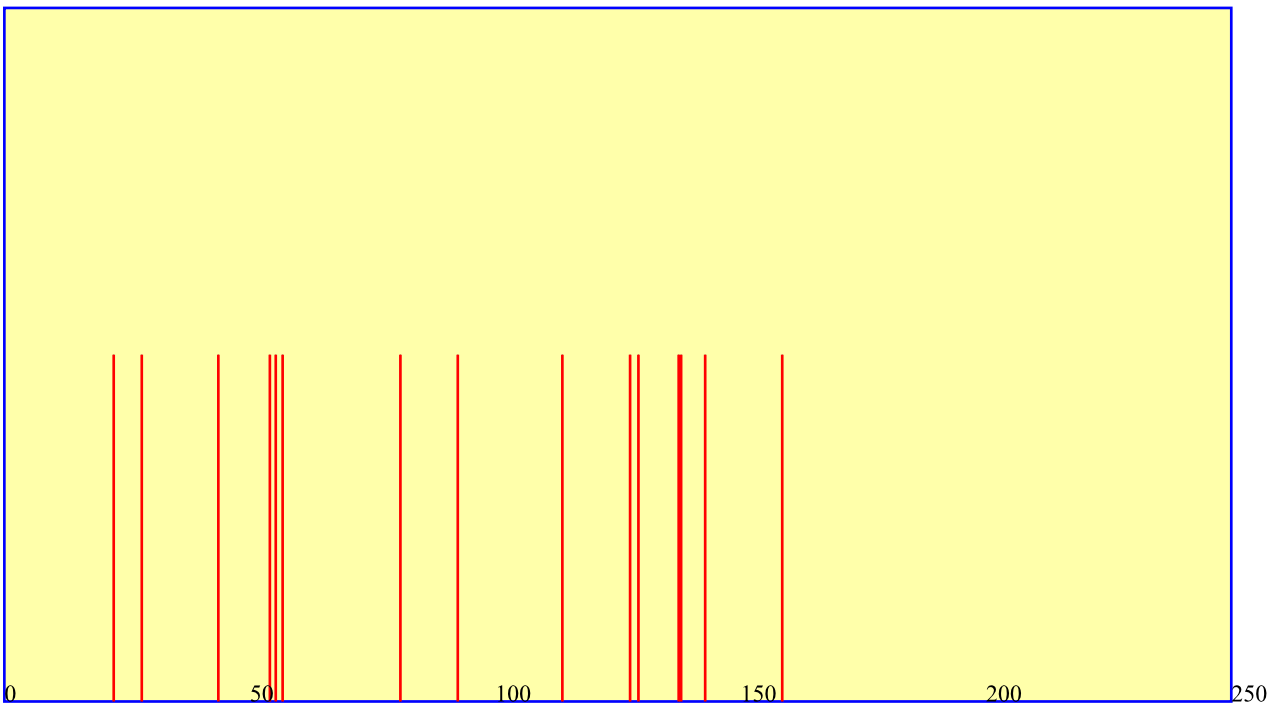
Preparation of (3R,aS)-tert-butyl 3-(4-iodophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(28)

Preparation of (3*R*,a*S*)-*tert*-butyl 3-(4-iodophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate28Following general procedure 3, CAN (11.6g, 21.1mmol) and**13**(5.75g, 10.1mmol) in 5:1 MeCN:H [2] O (90ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**28**(4.26g, 88perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) ***()***

HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

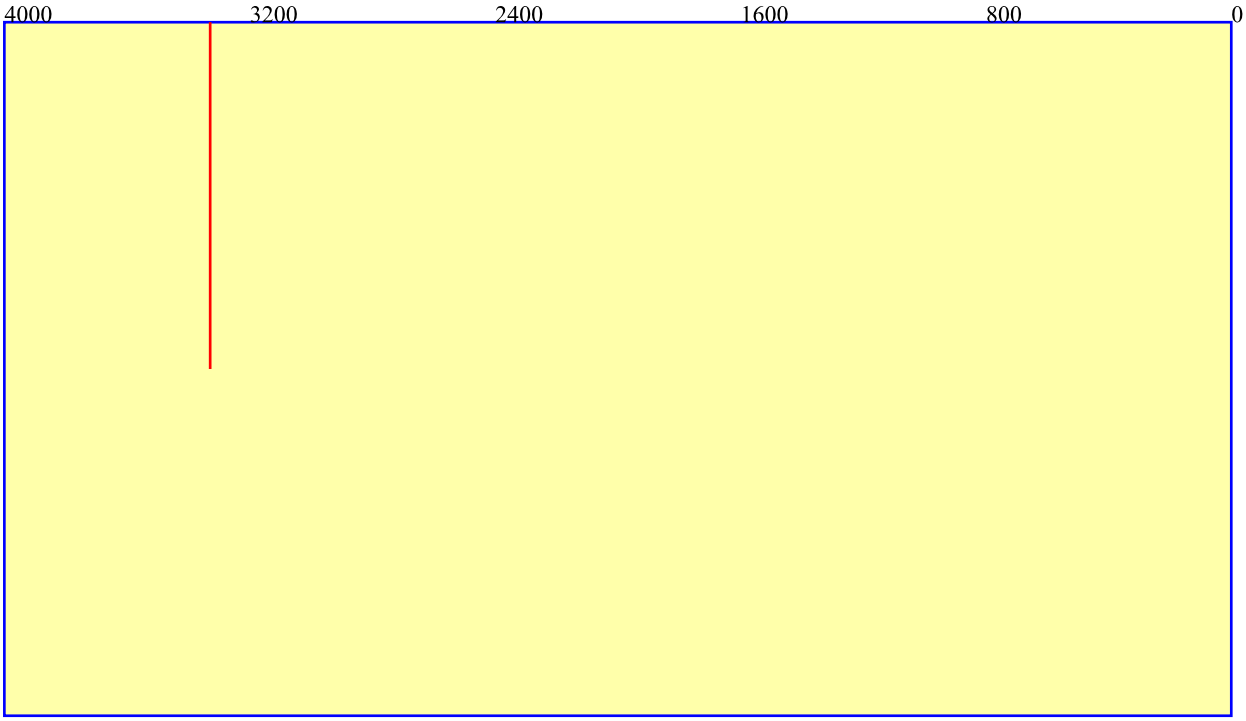


MS: APCI {+} *()()*
Found:
Formula:

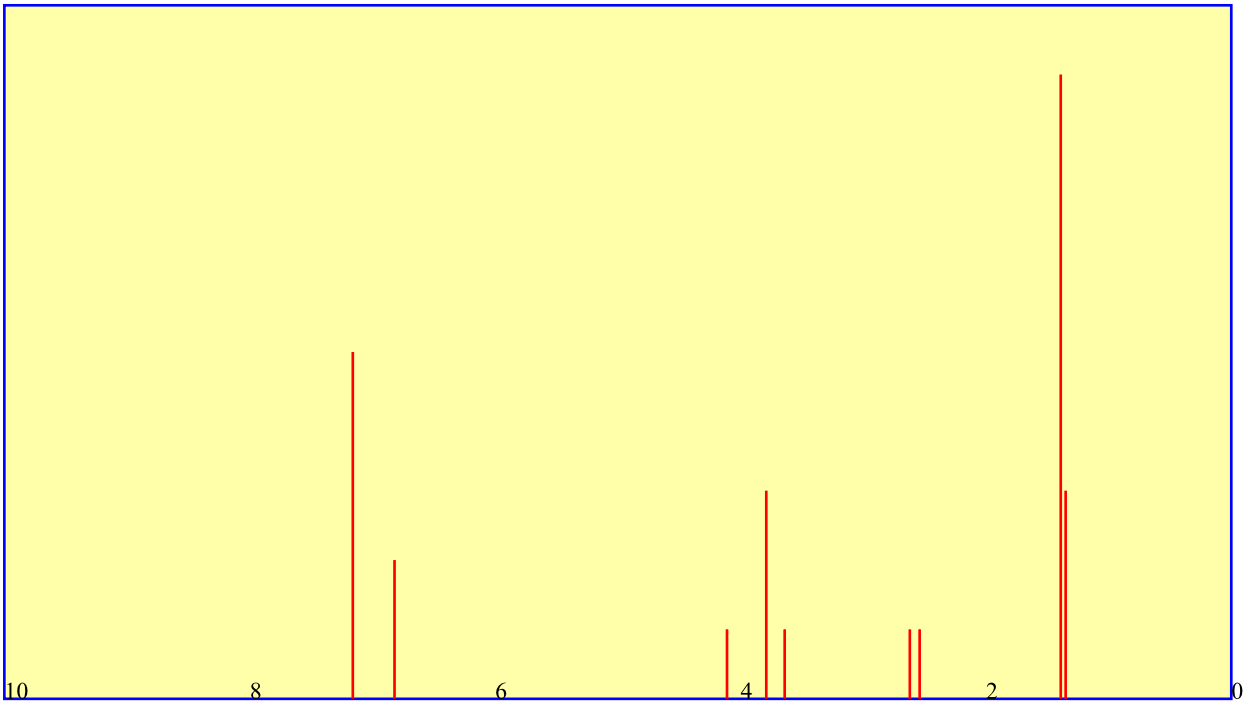
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(3-chlorophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(29)

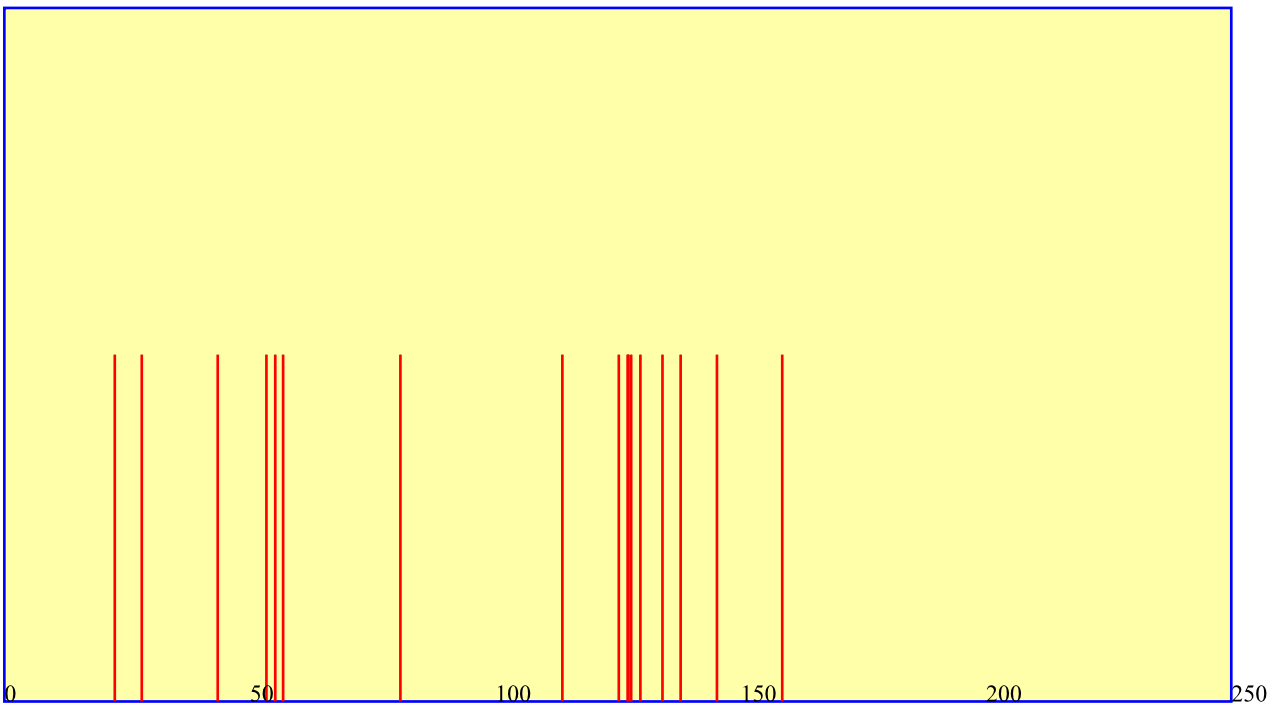
Preparation of (3*S*,a*R*)-*tert*-butyl 3-(3-chlorophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate29Following general procedure 3, CAN (2.45g, 4.56mmol) and**14**(1.04g, 2.17mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**29**(664mg, 79perc) as a clear oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



CNMR: 100 MHz *(CDCl [3])*

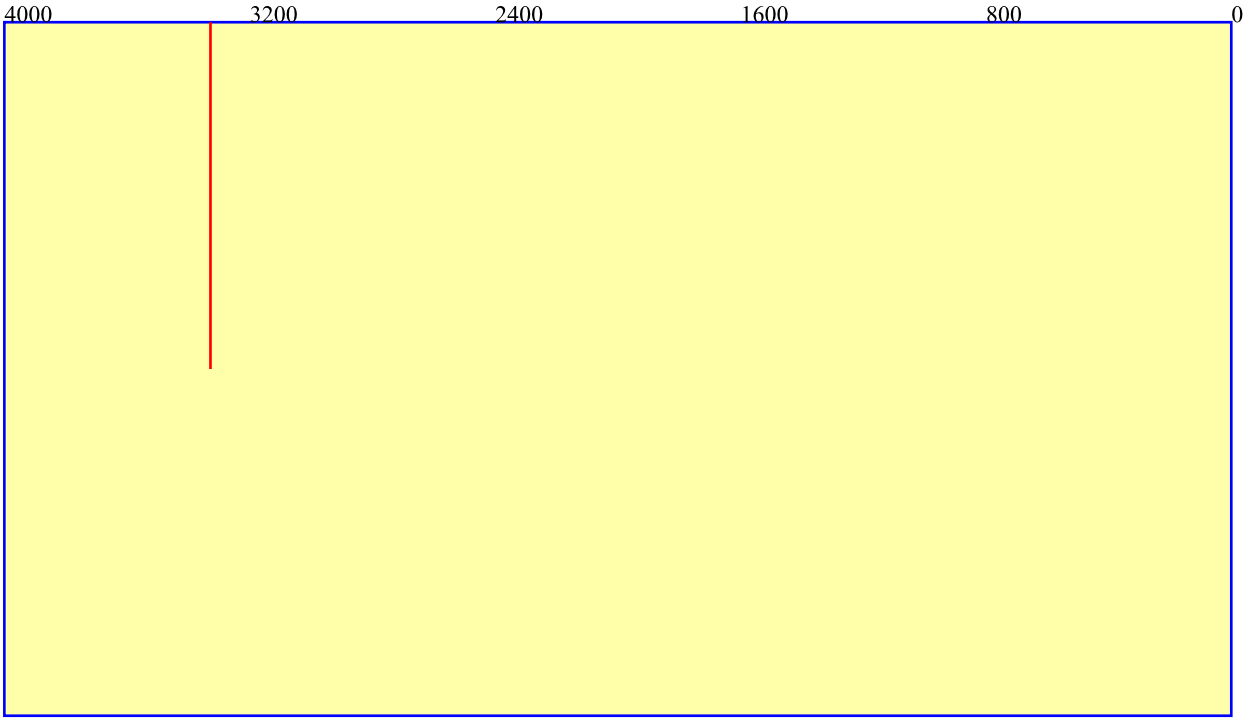


MS: APCI {+} *()()*
Found:
Formula:

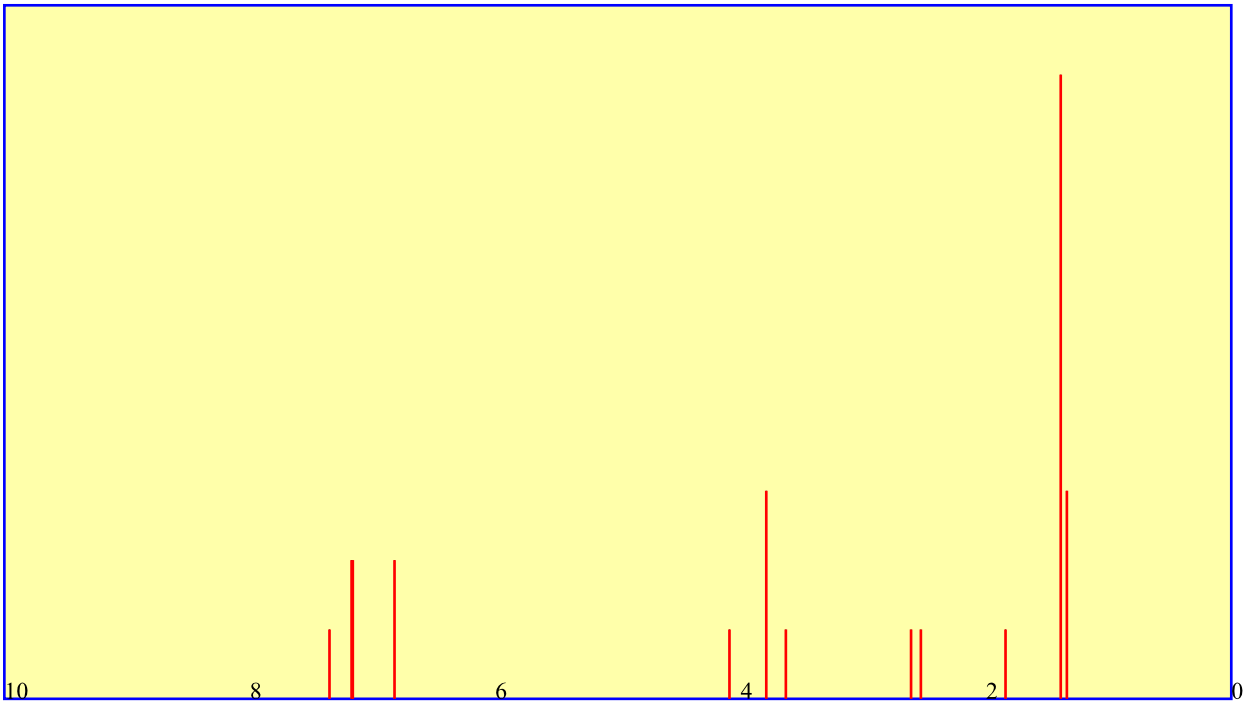
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(3-bromophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(30)

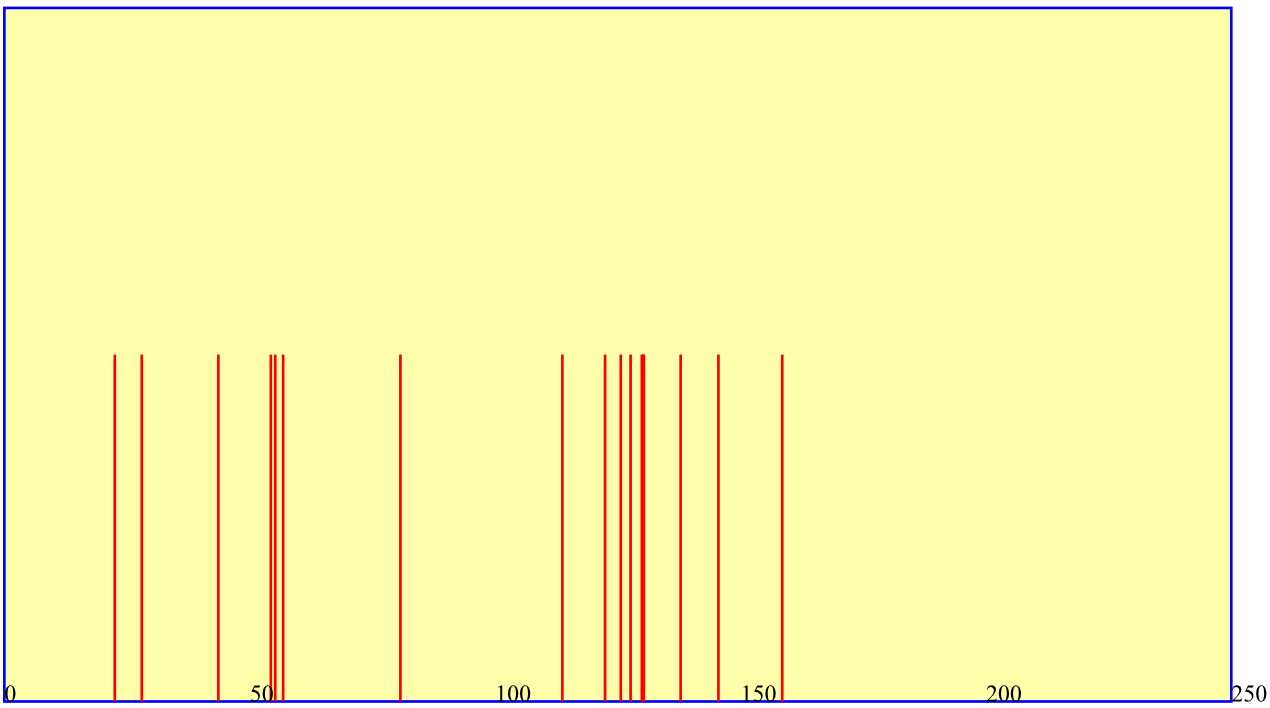
Preparation of (3*S*,a*R*)-*tert*-butyl 3-(3-bromophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate30Following general procedure 3, CAN (1.96g, 3.6mmol) and**16**(937mg, 1.8mmol) in 5:1 MeCN:H [2] O (24ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 8:1:1perc NEt [3]),**30**(621mg, 80perc) as a clear oil
OR: [a]D= (*c*,)
IR: (film) ***()***



HNMR: 400 MHz ***(CDCl [3])***



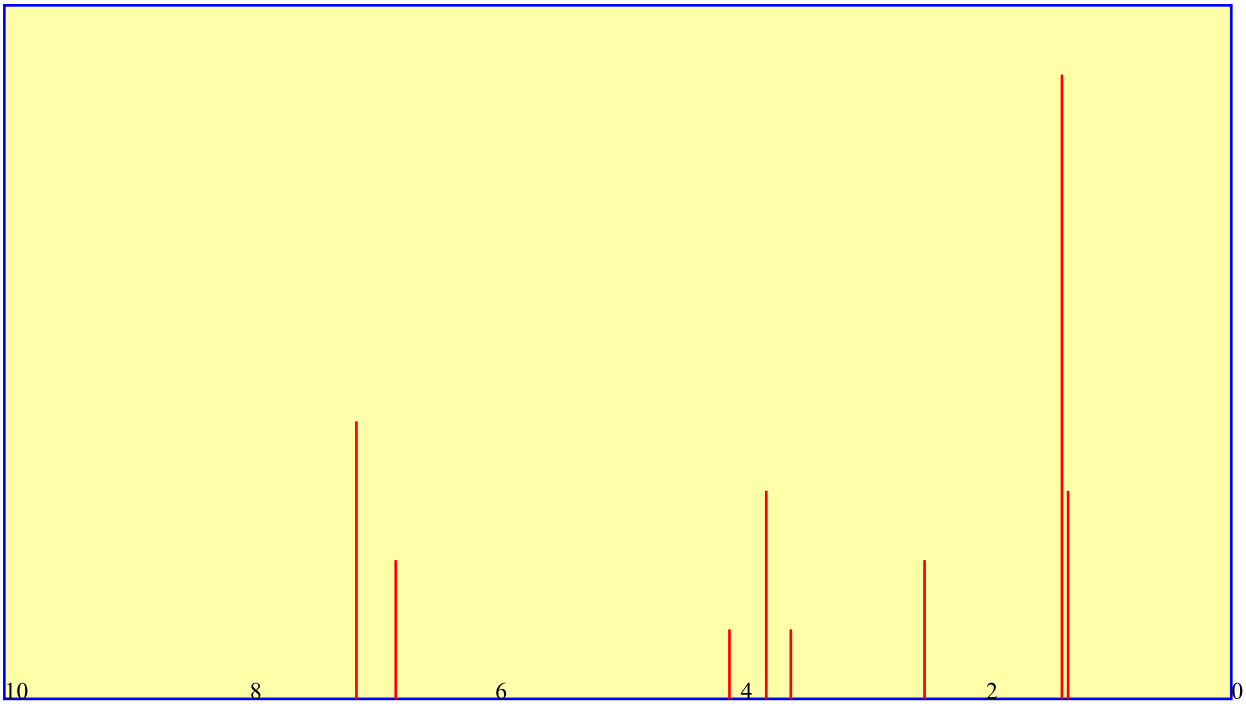
CNMR: 100 MHz *(CDCl [3])*



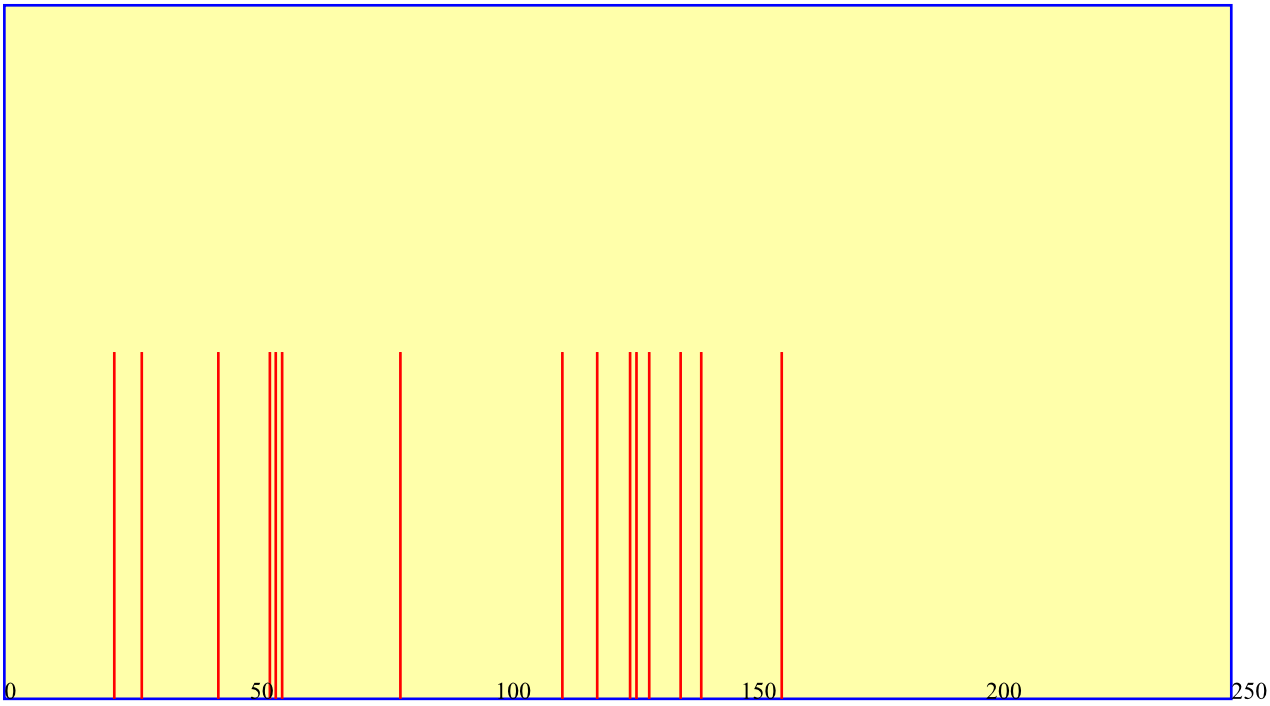
Preparation of (3S,aR)-tert-butyl 3-(4-bromophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(31)

Preparation of (3*S*,a*R*)-*tert*-butyl

-a-methyl-4-methoxybenzylamino)propanoate31Followingrepresentative procedure 3, CAN (2.20g, 4.0mmol) and**17**(1.0g, 1.9mmol) in MeCN:H [2] O 5:1 (9ml) gave, after work-up and column chromatography on silica gel (hexane:Et [2] O 5:1),**31**(595mg, 72perc) as a colourless oil
OR: [a]D= (*c*,)
HNMR: 400 MHz *(CDCl [3])*



CNMR: 50 MHz *(CDCl [3])*

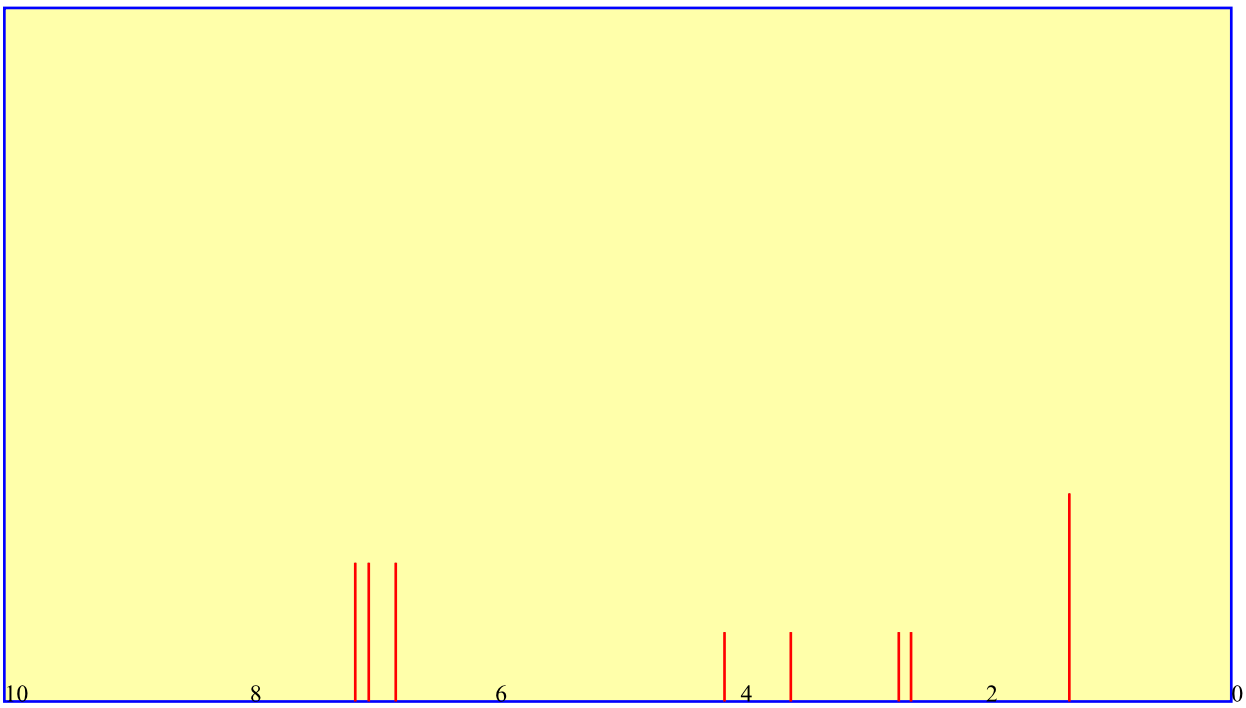


MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

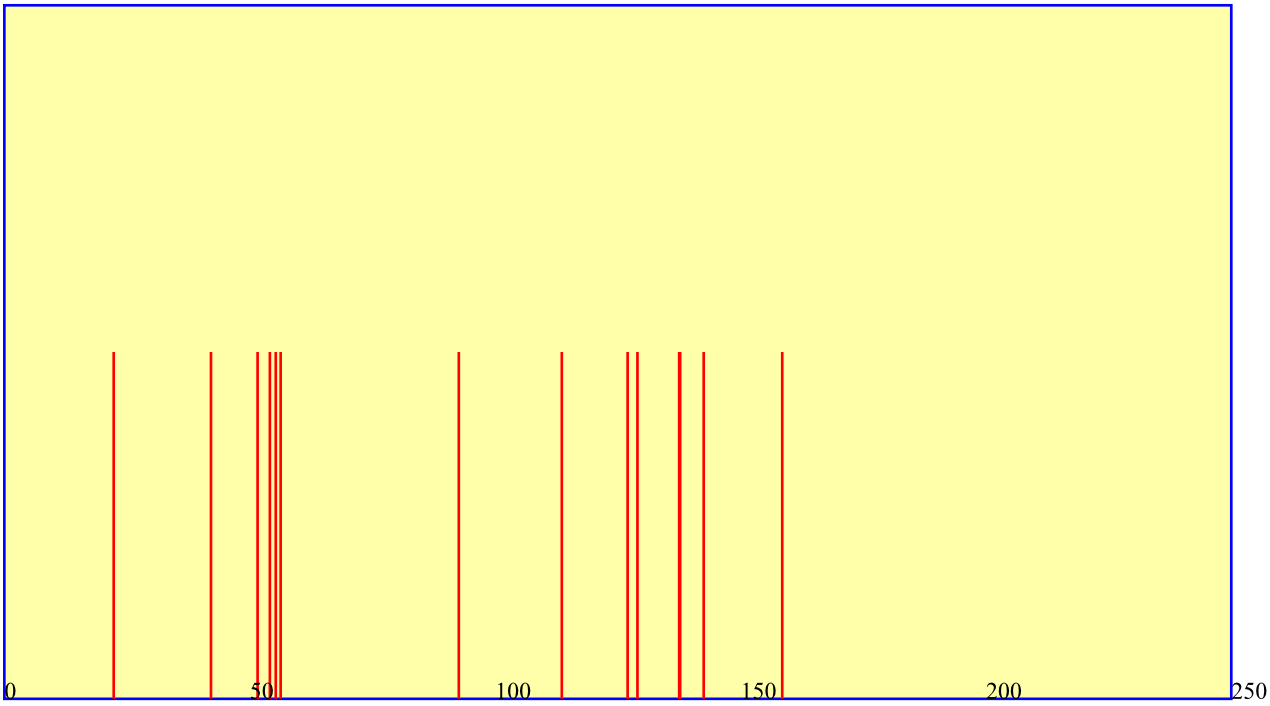
Preparation of (3R,aS)-methyl 3-(4-iodophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(32)

Preparation of (3*R*,a*S*)-methyl 3-(4-iodophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate32Following general procedure 5,**28**(3.0g, 6.24mmol) was added to a saturated solution of HCl in MeOH (20ml). Concentration*in vacuo*, recrystallisation (EtOAc:hexane) and treatment with saturated aqueous NaHCO [3] gave**32**(2.12g, 71perc) as a colourless oil; mp (HCl salt) 181-182C (EtOAc:hexane);freetextor[a] [D] {22} CHAR:821121.6 (c 1.2, CHCl [3])
IR: (film) *()*

HNMR: 400 MHz *(CDCl [3])*



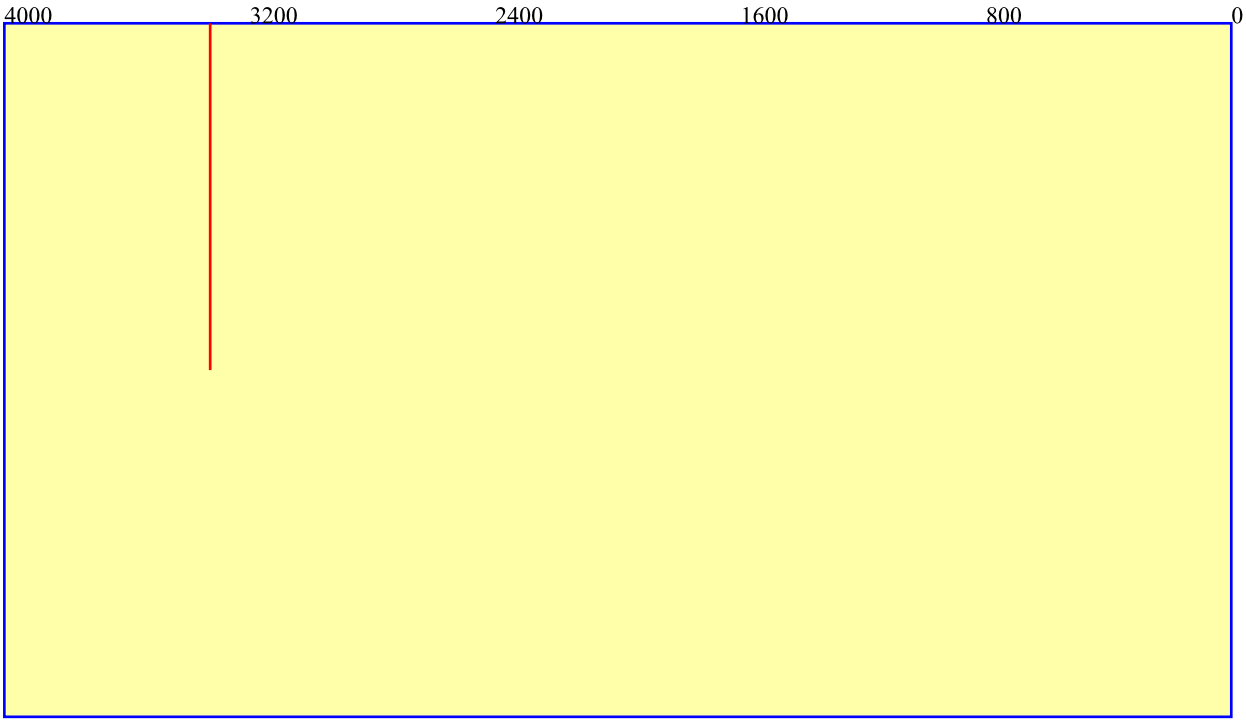
CNMR: 100 MHz *(CDCl [3])*



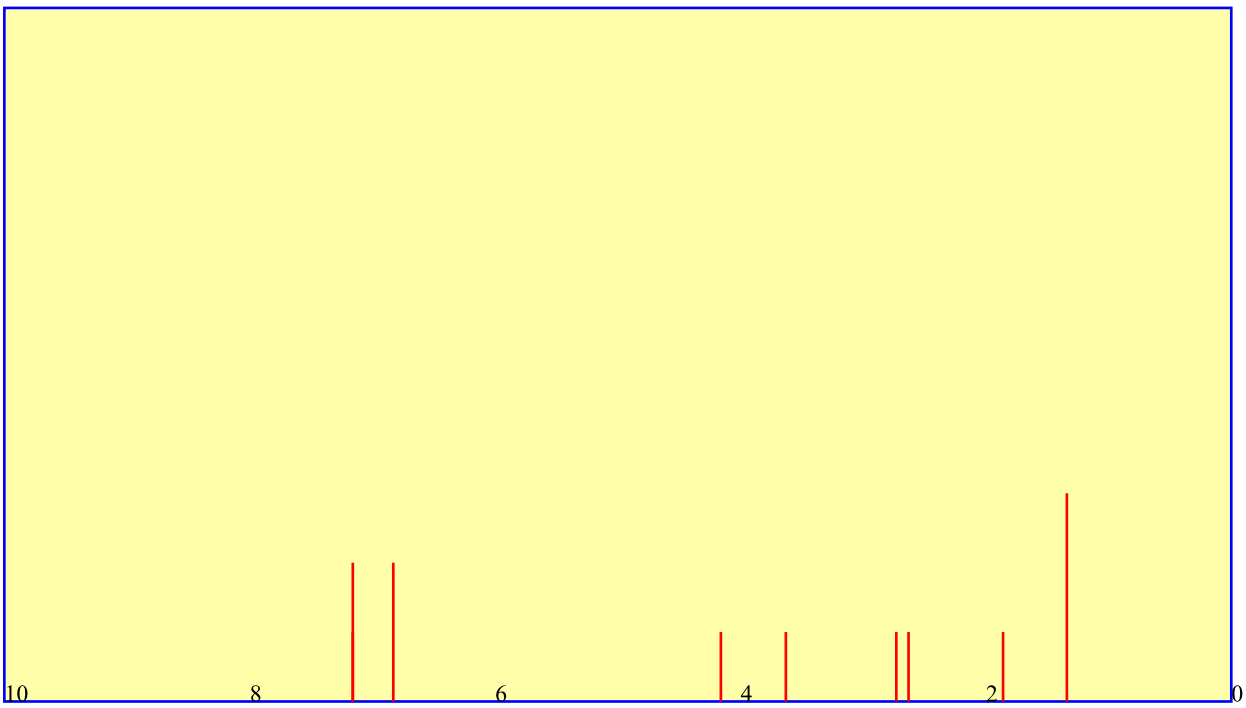
MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (3S,aR)-methyl 3-(3-chlorophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(33)

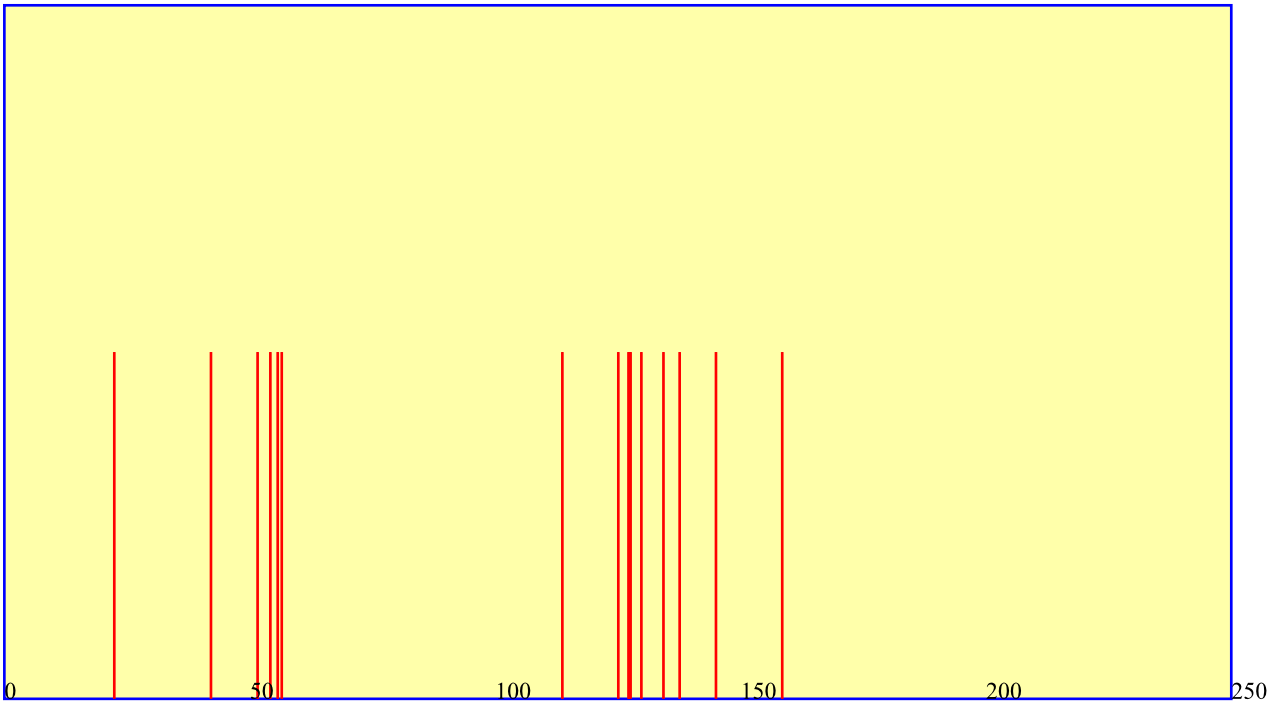
Preparation of (3*S*,a*R*)-methyl 3-(3-chlorophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate33Following general procedure 5,**29**(1.89g, 4.87mmol) was added to a saturated solution of HCl in MeOH (20ml). Concentration*in vacuo*, recrystallisation (EtOAc:hexane) and treatment with saturated aqueous NaHCO [3] gave**33**(1.48g, 79perc) as a colourless oil; mp (HCl salt) 169-170C (EtOAc:hexane)
OR: [a]D= (*c*,)
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

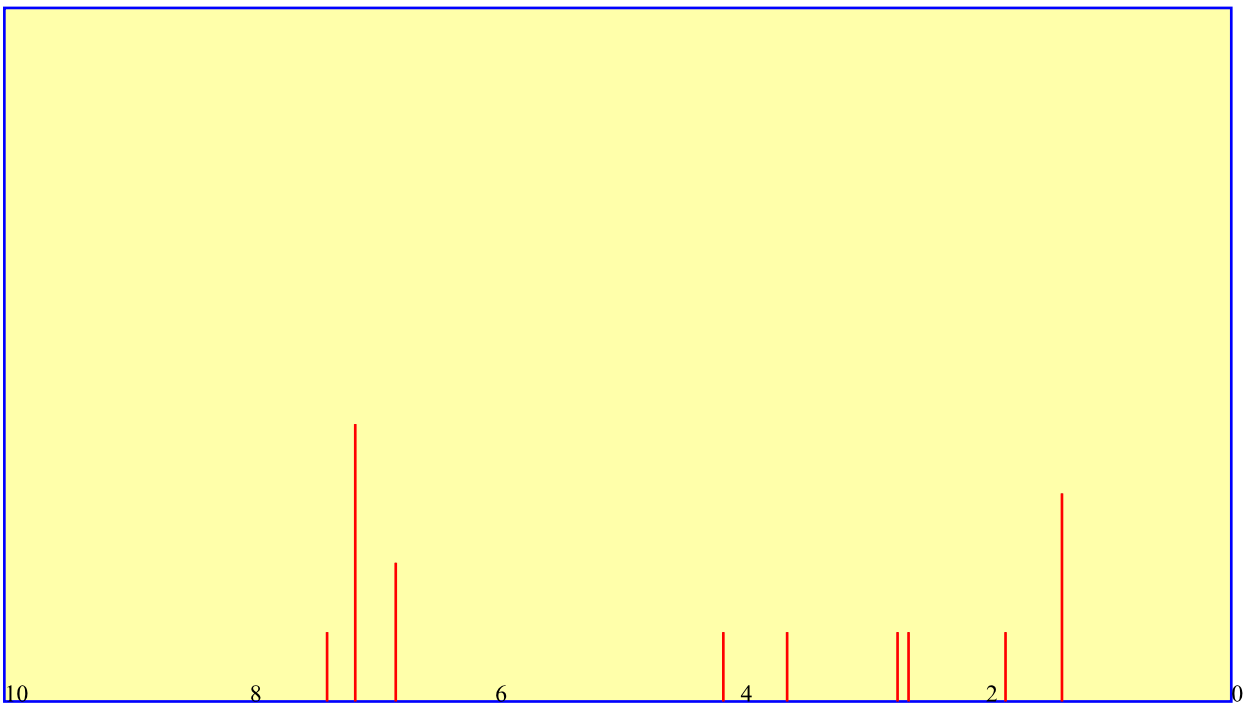


MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

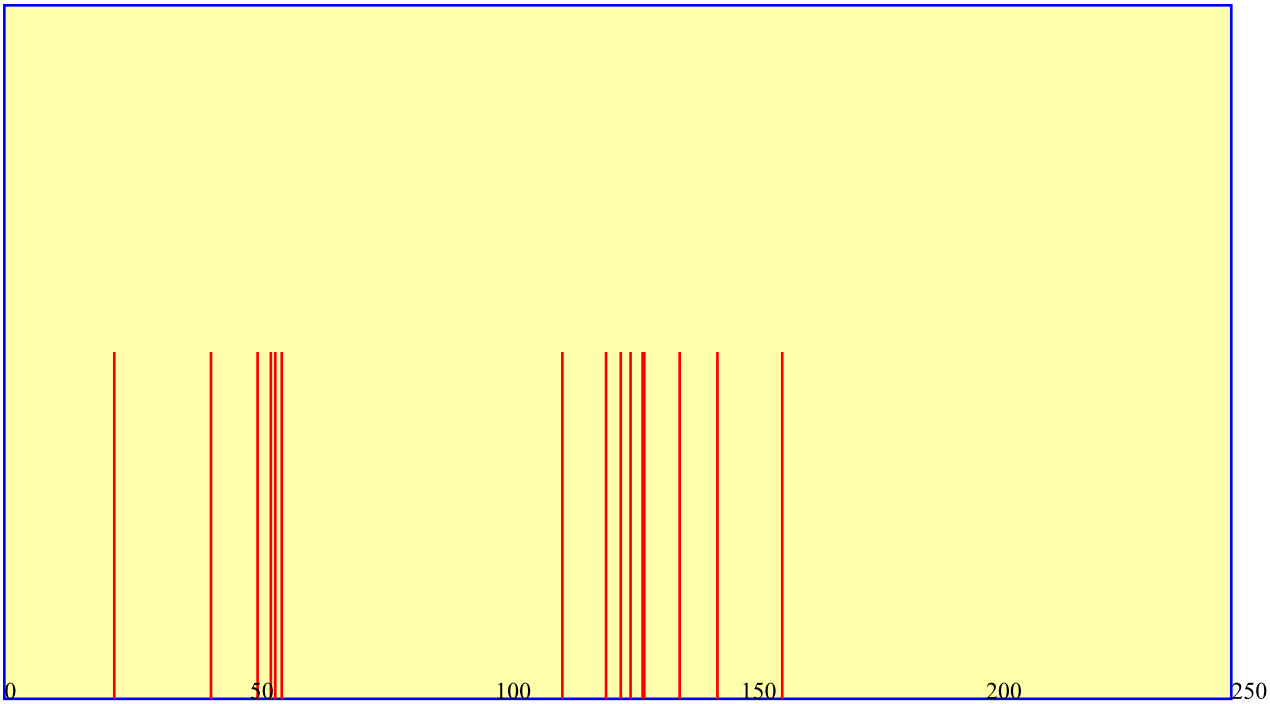
Preparation of (3S,aR)-methyl 3-(3-bromophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(34)

Preparation of (3*S*,a*R*)-methyl 3-(3-bromophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate34Following general procedure 5,**30**(750mg, 1.73mmol) was added to a saturated solution of HCl in MeOH (20ml). Concentration*in vacuo*, recrystallisation (EtOAc:hexane) and treatment with saturated aqueous NaHCO [3] gave**34**(487mg, 66perc)as a colourless oil
OR: [a]D= (*c*,)
IR: (film) *()*

HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

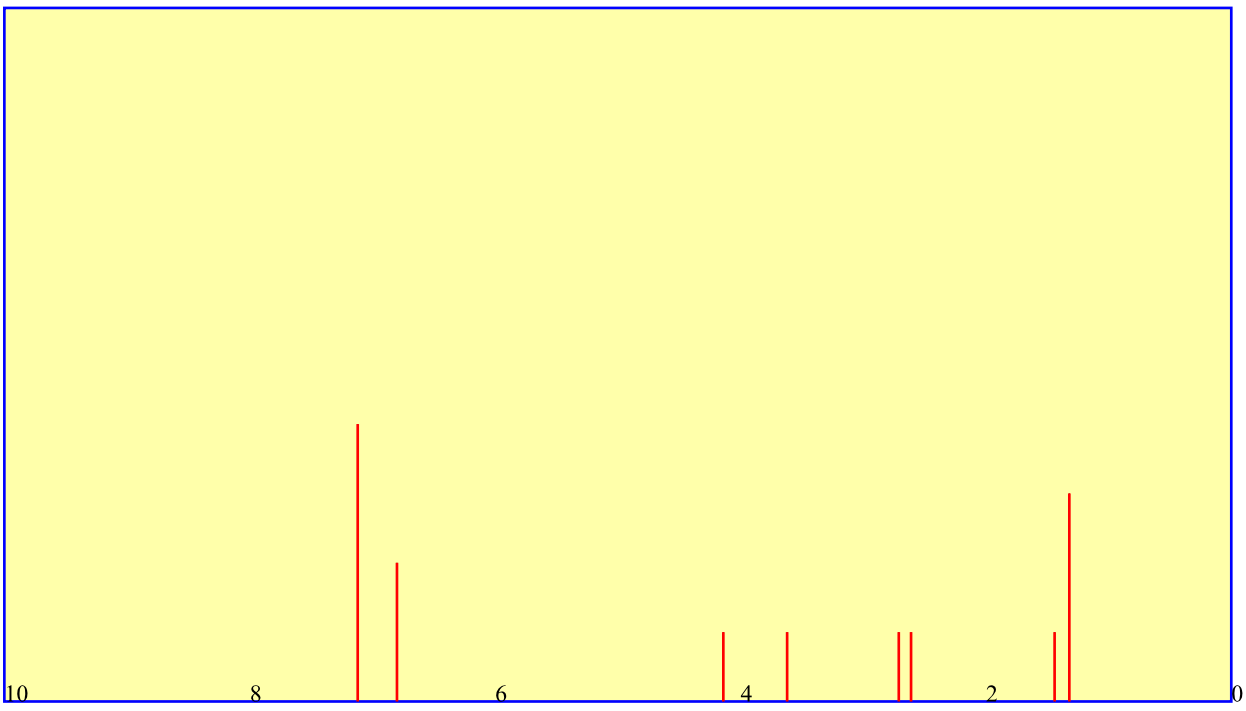


MS: CI {+} ***()()***
Found:
Formula:
method:
Required:
overall:

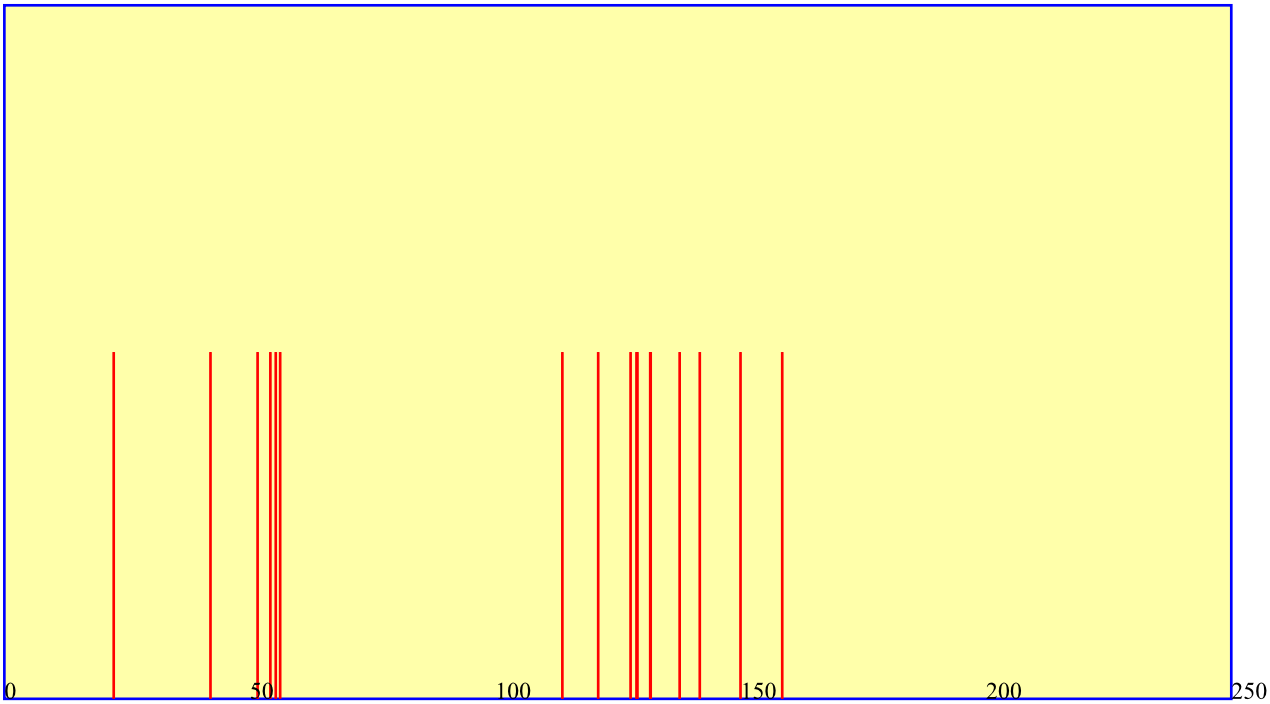
Preparation of (3S,aR)-methyl 3-(4-bromophenyl)-3-(N-a-methyl-4-methoxybenzylamino)propanoate(35)

Preparation of (3*S*,a*R*)-methyl 3-(4-bromophenyl)-3-(*N*-a-methyl-4-methoxybenzylamino)propanoate35Following general procedure 5,**31**(2.2g, 5.08mmol) was added to a saturated solution of HCl in MeOH (75ml). Concentration*in vacuo*, recrystallisation (EtOAc:hexane) and treatment with saturated aqueous NaHCO [3] gave**35**(1.45g, 73perc)as a colourless oil
OR: [a]D= (*c*,)
IR: (film) ***()***

HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

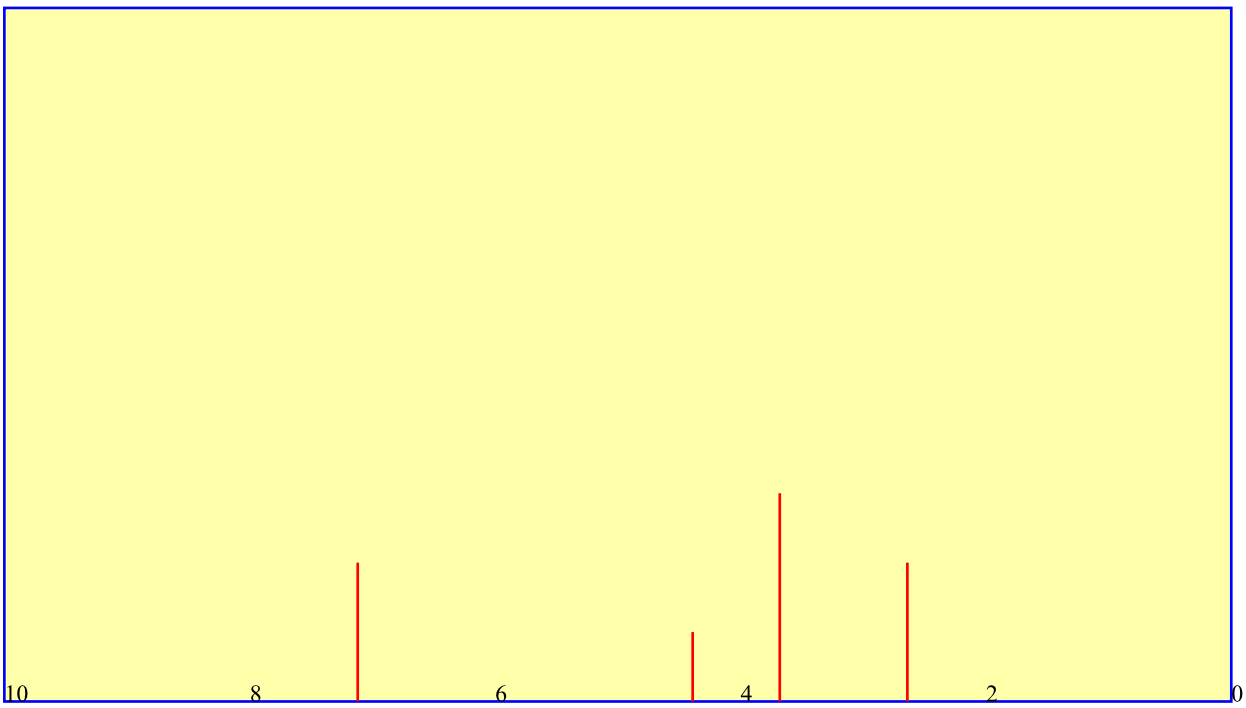


MS: CI {+} *()()*
Found:
Formula:
method:
Required:
overall:

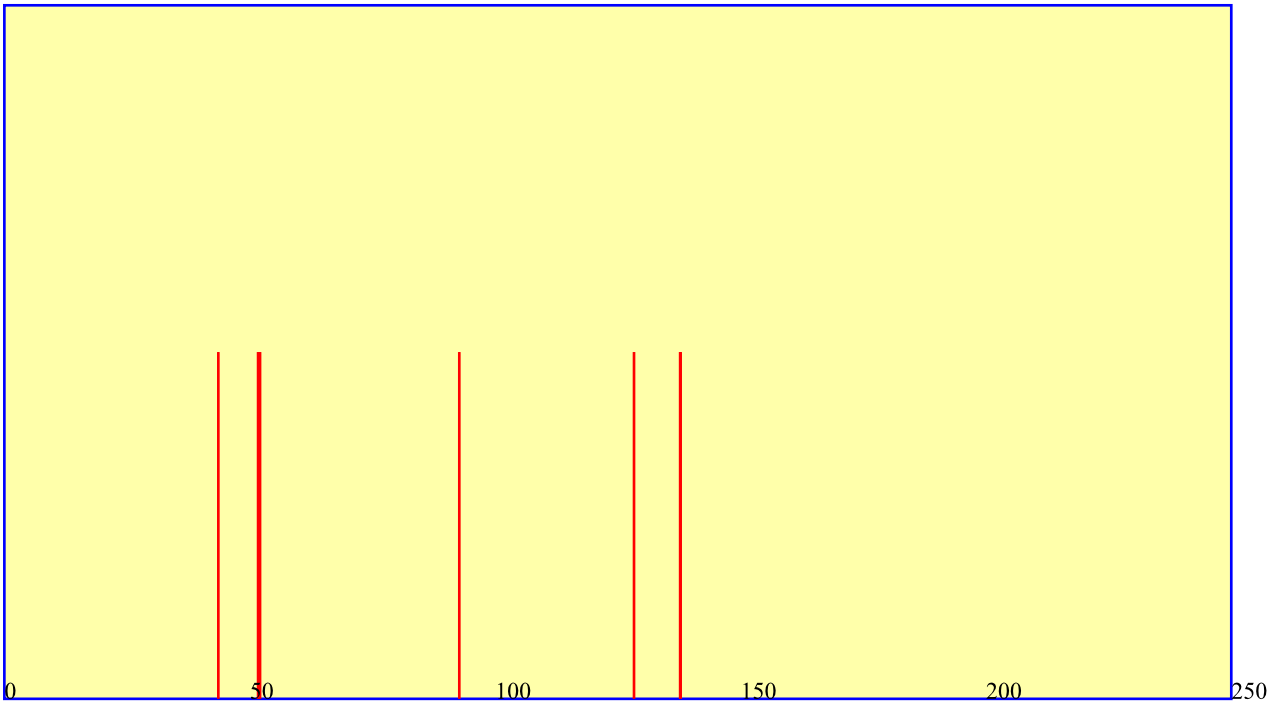
Preparation of (R)-methyl 3-(4-iodophenyl)-3-aminopropanoate(36)

Preparation of (*R*)-methyl 3-(4-iodophenyl)-3-aminopropanoate36Following general procedure 4, CAN (1.0g, 1.84mmol) and**32**(200mg, 0.46mmol) in 5:1 MeCN:H [2] O (6ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:2),**36**(85mg, 61perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) *()*

HNMR: 400 MHz *(CDCl [3])*



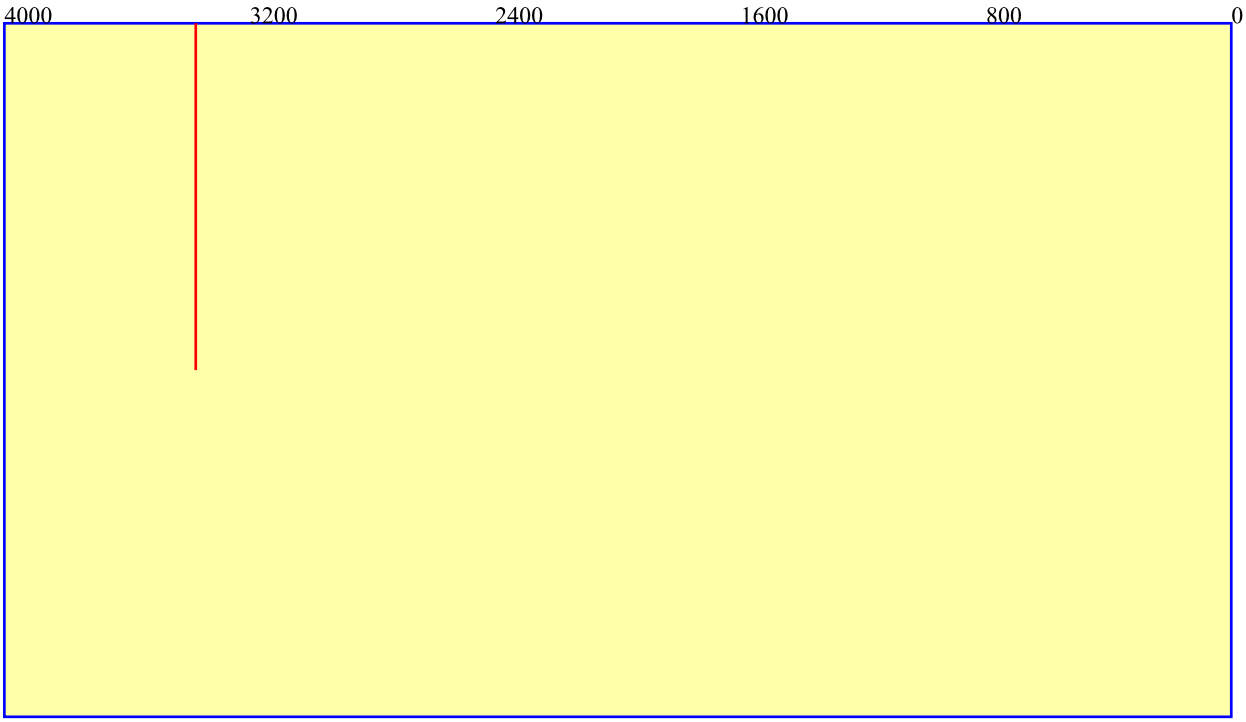
CNMR: 100 MHz *(CDCl [3])*



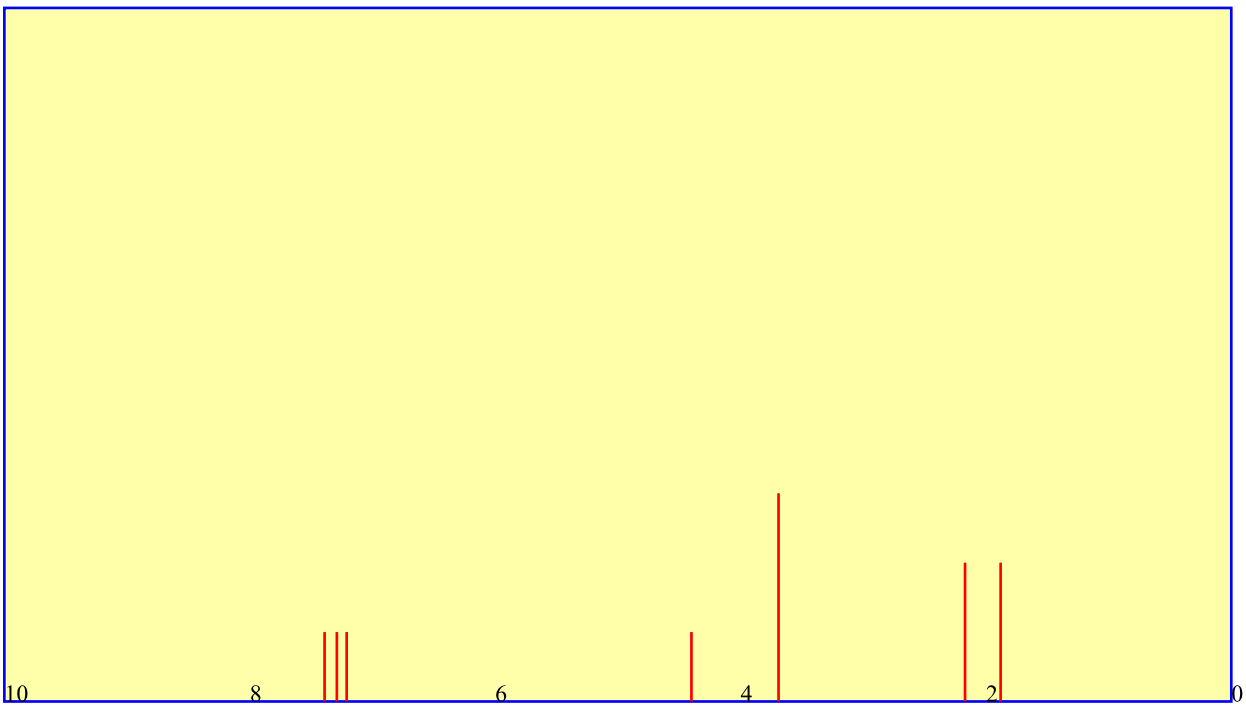
MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (S)-methyl 3-(3-chlorophenyl)-3-aminopropanoate(37)

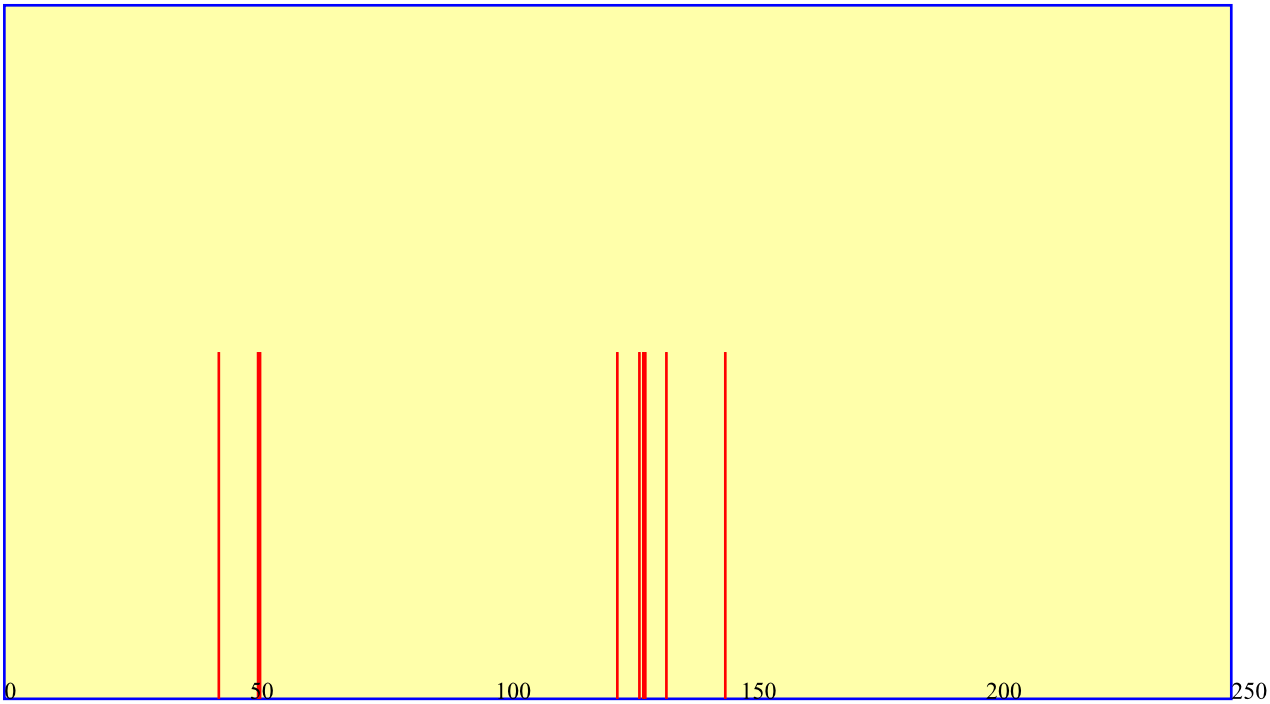
Preparation of (*S*)-methyl 3-(3-chlorophenyl)-3-aminopropanoate37Following general procedure 4, CAN (2.58g, 4.70mmol) and**33**(408mg, 1.18mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:2),**37**(135mg, 54perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



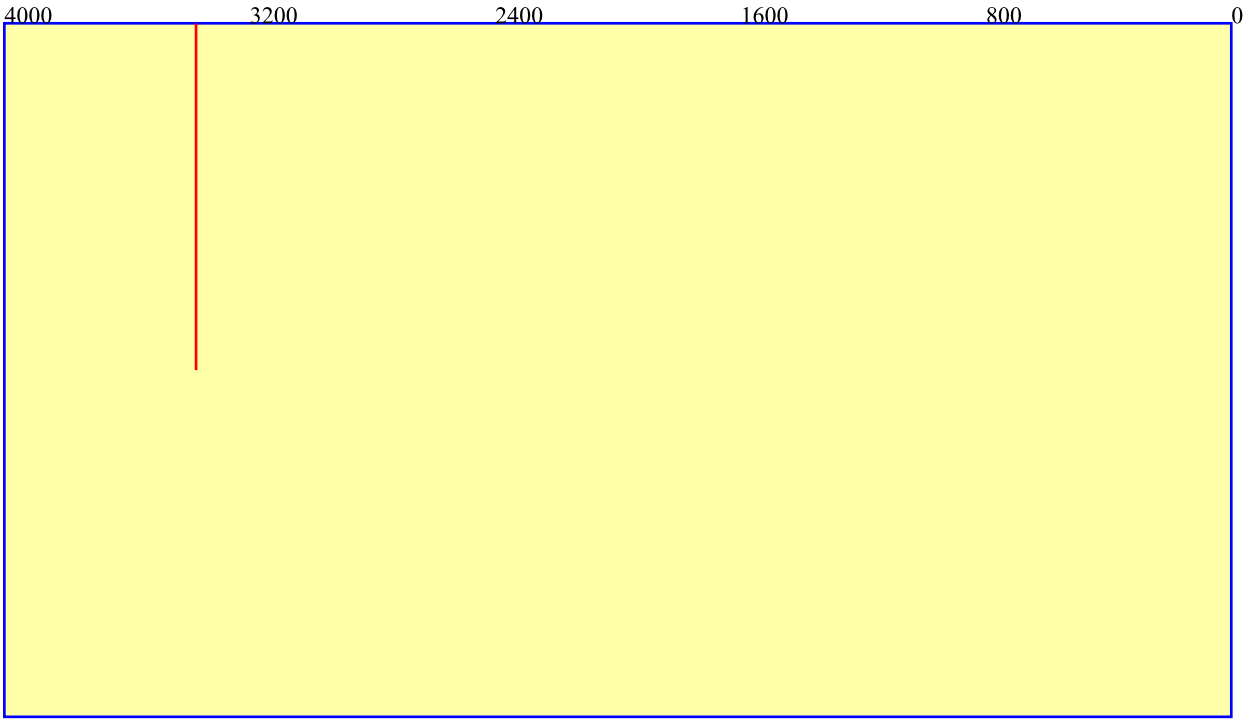
CNMR: 100 MHz *(CDCl [3])*



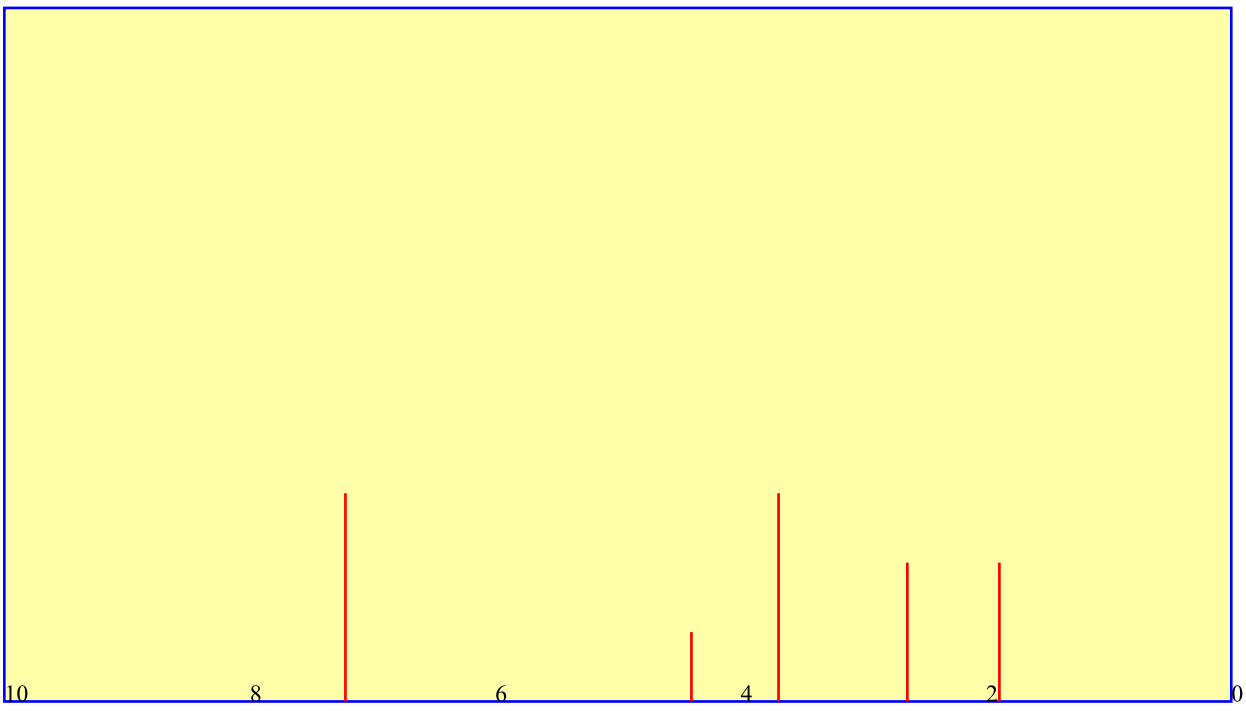
MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (S)-methyl 3-(3-bromophenyl)-3-aminopropanoate(38)

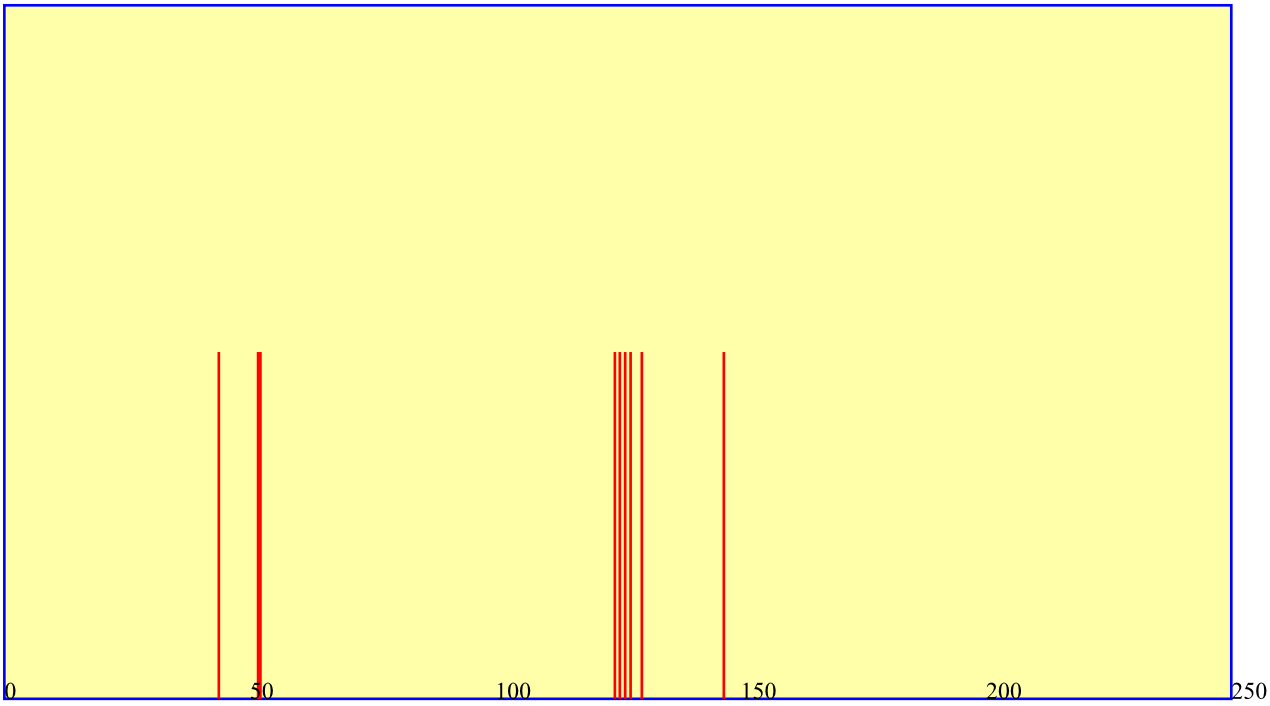
Preparation of (*S*)-methyl 3-(3-bromophenyl)-3-aminopropanoate38Following general procedure 4, CAN (1.90g, 3.46mmol) and**34**(338mg, 0.86mmol) in 5:1 MeCN:H [2] O (12ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:2),**38**(114mg, 51perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) *()*



HNMR: 400 MHz *(CDCl [3])*



CNMR: 100 MHz *(CDCl [3])*

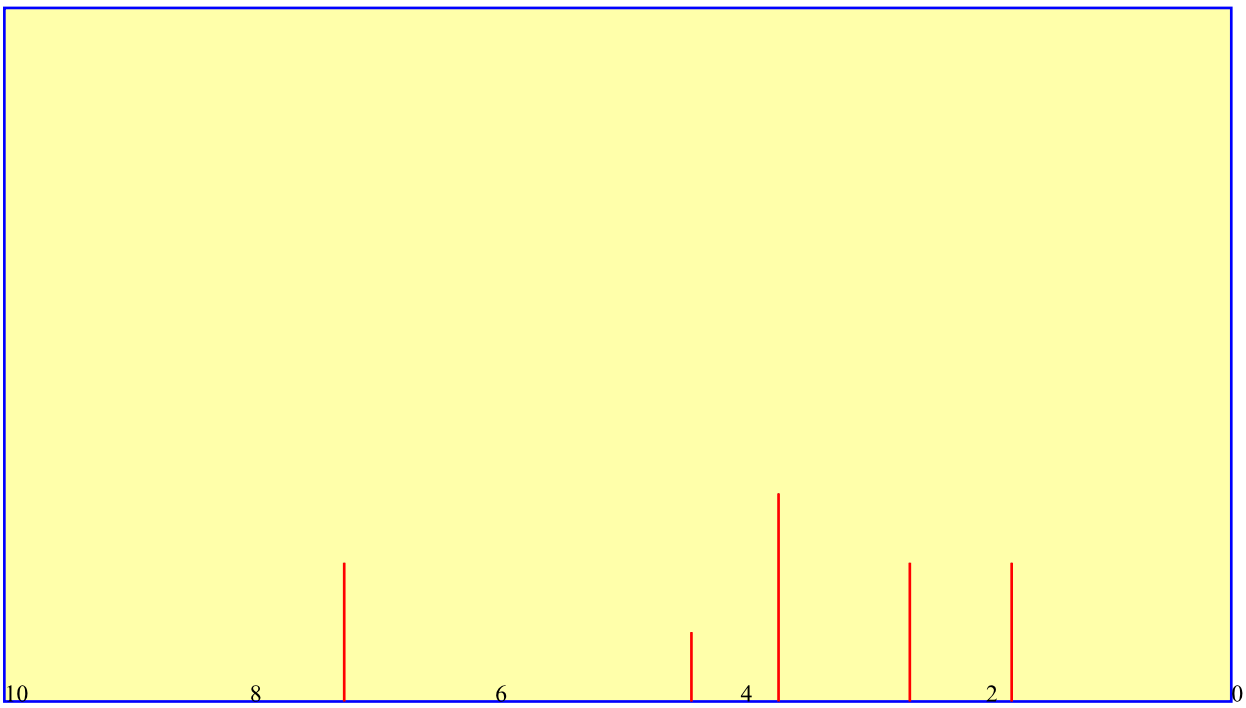


MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

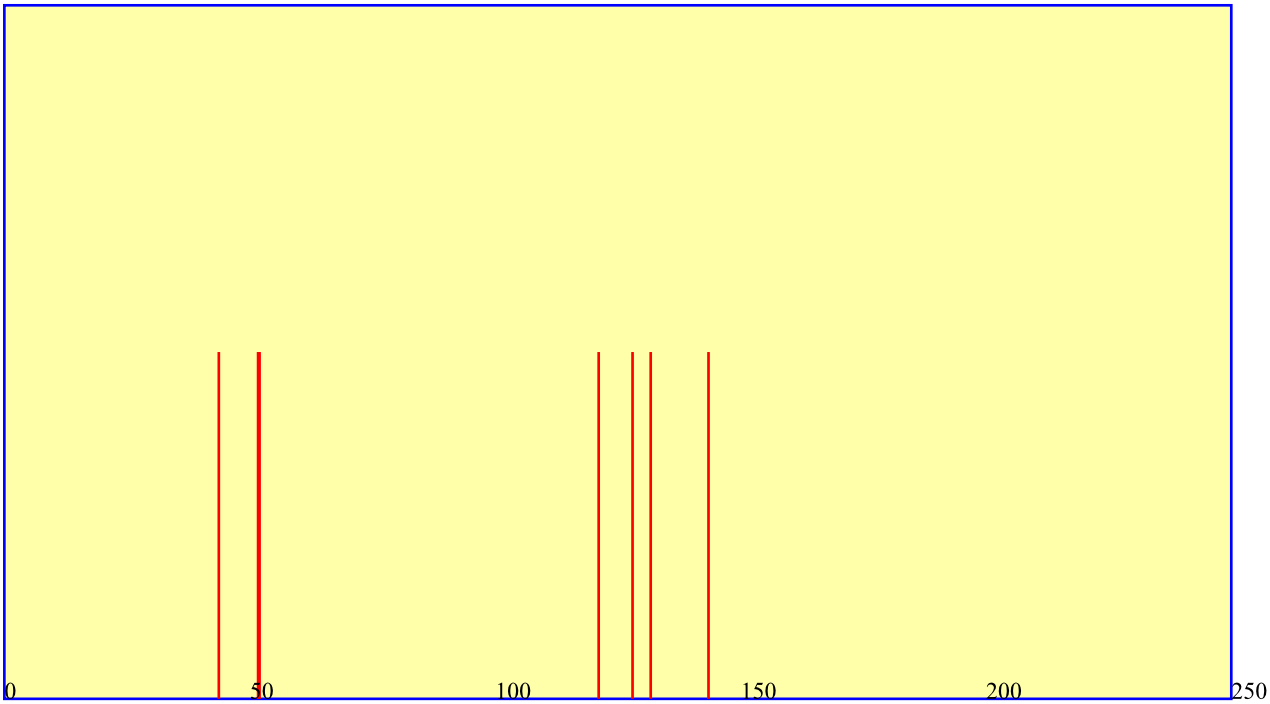
Preparation of (S)-methyl 3-(4-bromophenyl)-3-aminopropanoate(39)

Preparation of (*S*)-methyl 3-(4-bromophenyl)-3-aminopropanoate39Following general procedure 4, CAN (2.79g, 5.08mmol) and**35**(500mg, 1.27mmol) in 5:1 MeCN:H [2] O (18ml) gave, after work up and purification by column chromatography on silica gel (hexane:Et [2] O 1:1),**39**(172mg, 52perc) as a yellow oil
OR: [a]D= (*c*,)
IR: (film) *()*

HNMR: 400 MHz *(CDCl [3])*



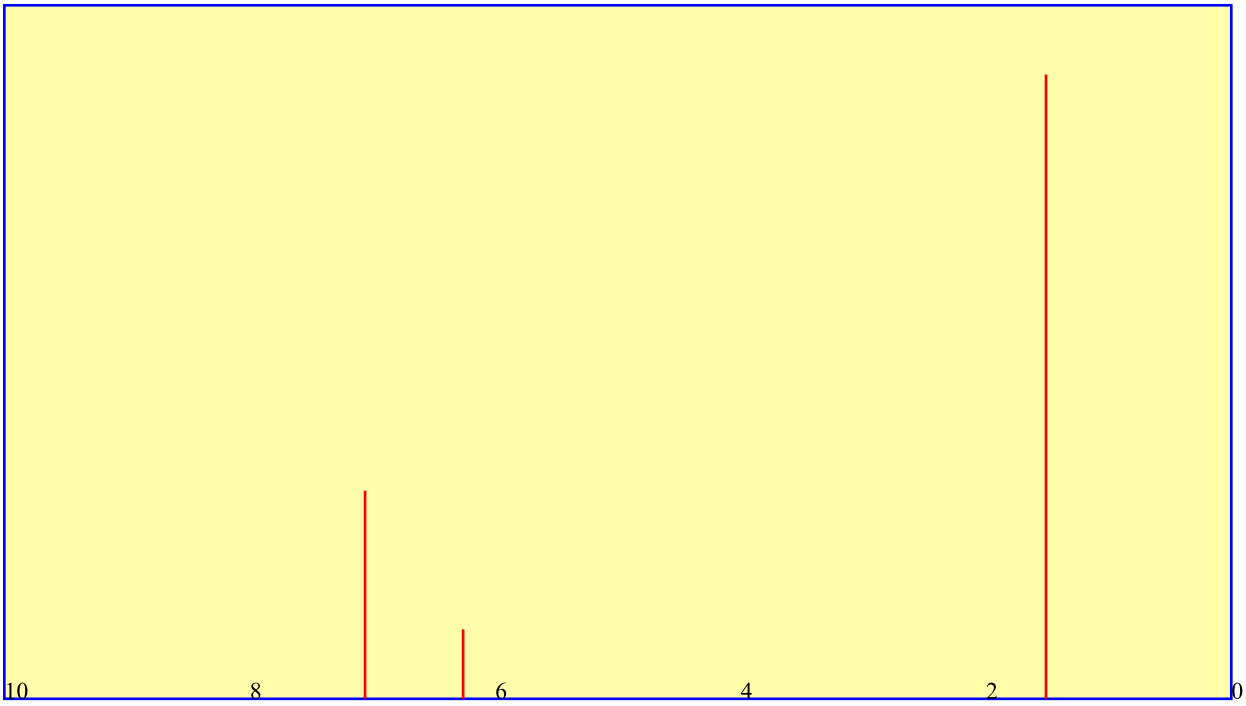
CNMR: 100 MHz *(CDCl [3])*



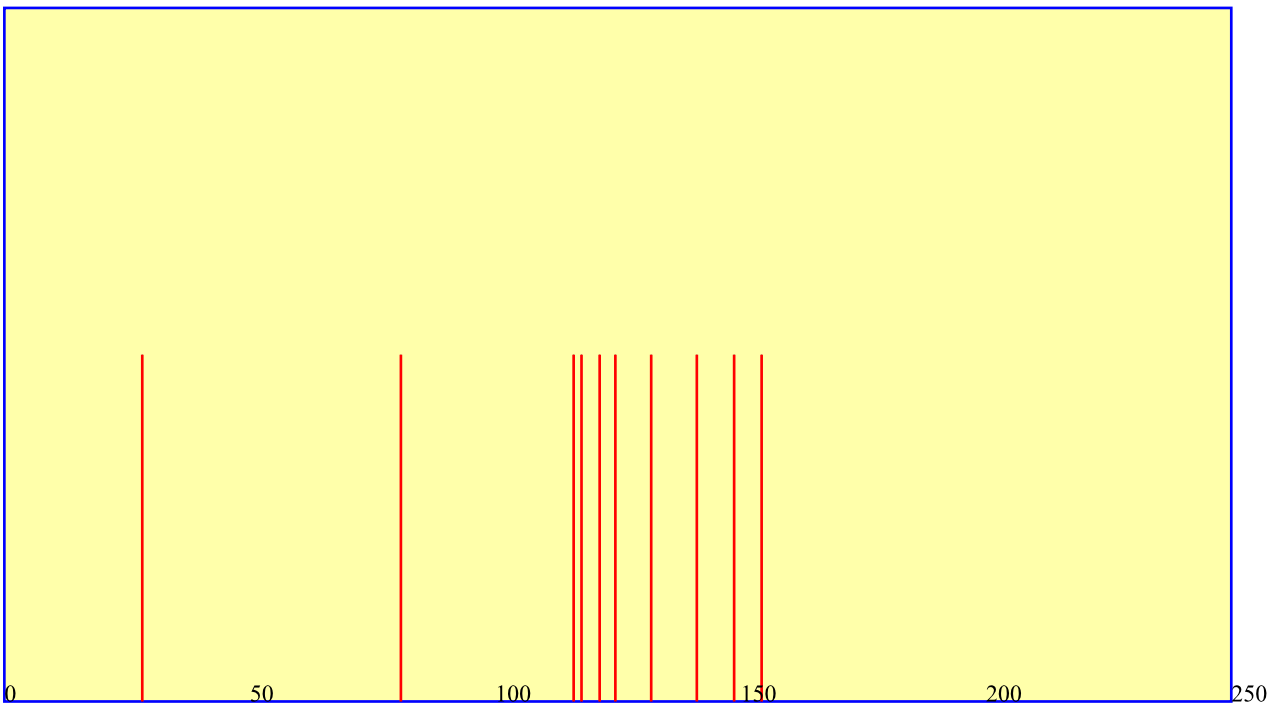
MS: APCI {+} *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of(E)-tert-butyl 3-(3,4-difluorophenyl)prop-2-enoate(40)

Preparation of*(E)-tert*-butyl 3-(3,4-difluorophenyl)prop-2-enoate40(*tert*-butoxycarbonylmethylene)triphenylphosphorane (5.79g, 15.4mmol, 1.1eq) was added to a stirred solution of 3,4-difluorobenzaldehyde (1.98g, 14.0mmol, 1.0eq) in DCM (20ml) under nitrogen at RT and stirred for sixteen hours before being diluted with DCM (30ml) and concentrated*in vacuo*. Purification by column chromatography on silica gel (hexane:Et [2] O 30:1) yielded a partially separable mixture of stereoisomers. The (*E*) isomer was purified to homogeneity by recrystallization (hexane:Et [2] O) to give**40**as white needles (3.5g, 88perc); m.p. 61CHAR:730C (hexane:Et [2] O); Found C, 64.9; H, 5.6perc; C [13] H [14] F [2] O [2] requires C, 65.0; H, 5.9perc;*v* [max] (KBr) 2979, 2927 (C-H), 1701 (C=O), 1640 (C=C), 1150 (C-O)
HNMR: 400 MHz *(CDCl [3])*



CNMR: 50 MHz *(CDCl [3])*

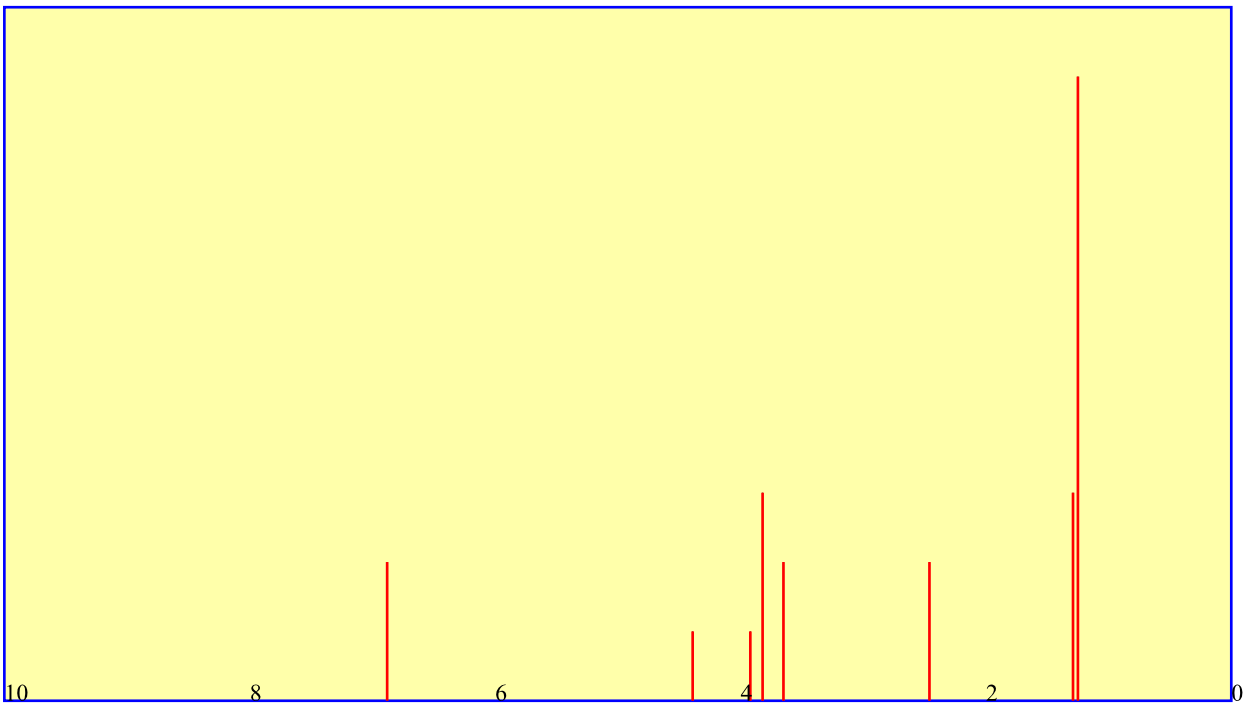


MS: CI, NH [3] *()()*
Found:
Formula:

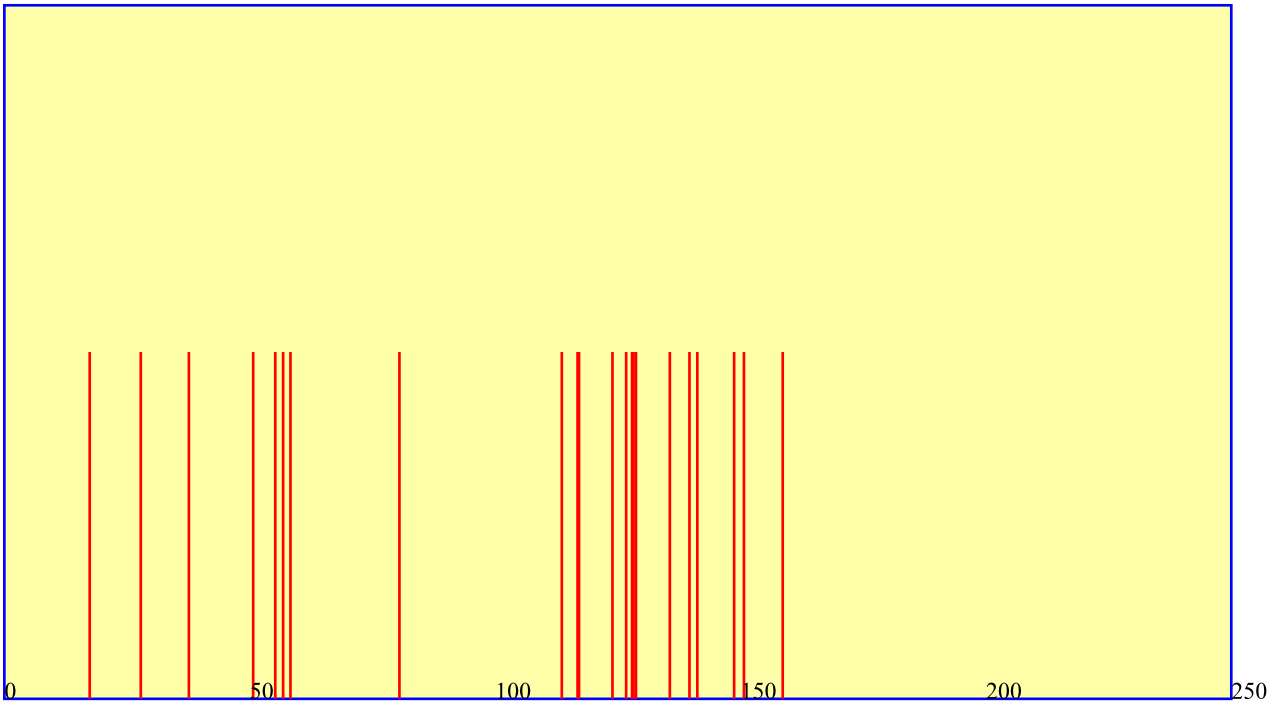
method:
Required:
overall:

Preparation of (3S,aR)-tert-butyl 3-(3,4-difluorophenyl)-3-(N-benzyl-N-a-methylbenzyl)propanoate(41)

Preparation of (3*S*,a*R*)-*tert*-butyl 3-(3,4-difluorophenyl)-3-(*N*-benzyl-*N*-a-methylbenzyl)propanoate41Following representative procedure**2**,*n*-BuLi (8.64mL, 2.5M 21.6mmol), (*R*)-**1**(5.37g, 22.3mmol) in THF (15mL) and (*E*)-**40**(3.36g, 14.0mmol) gave, after purification by column chromatography on silica gel (hexane:Et [2] O 15:1) and recrystallisation (Et [2] O:hexane),**41**as white crystals (5.8g, 86perc)
OR: [a]D= (*c*,)
HNMR: 400 MHz *(CDCl [3])*



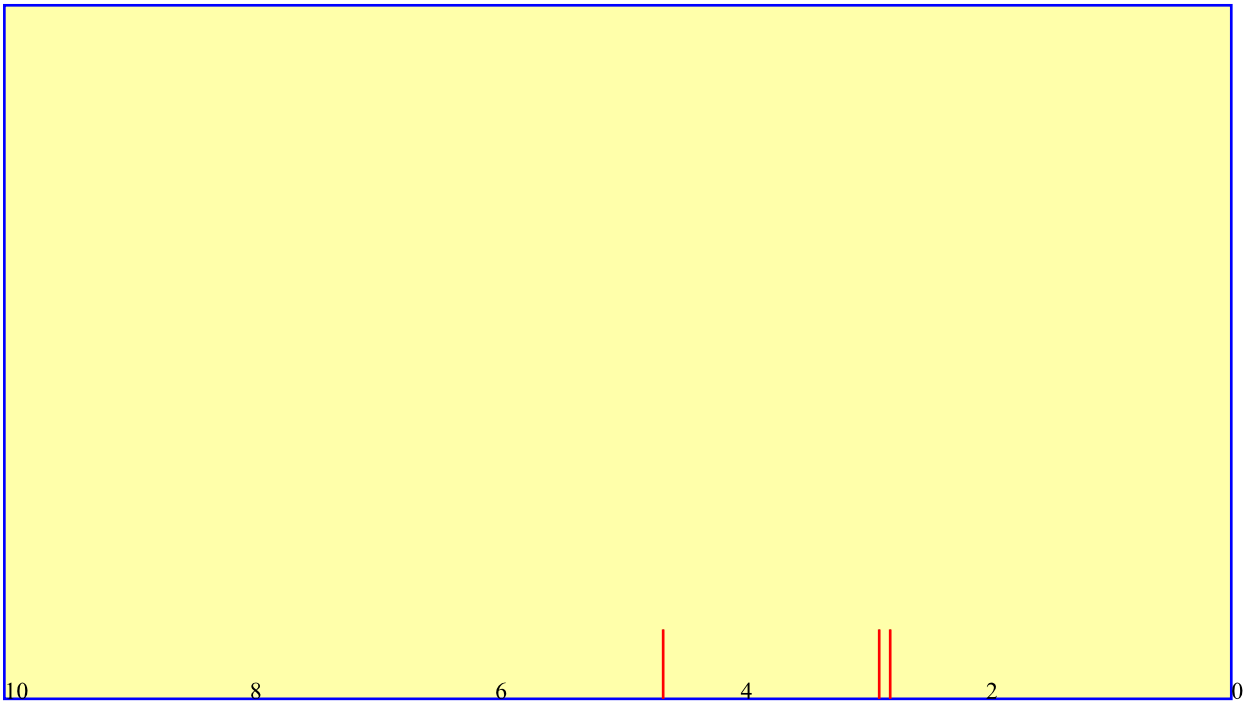
CNMR: 125 MHz *(CDCl [3])*



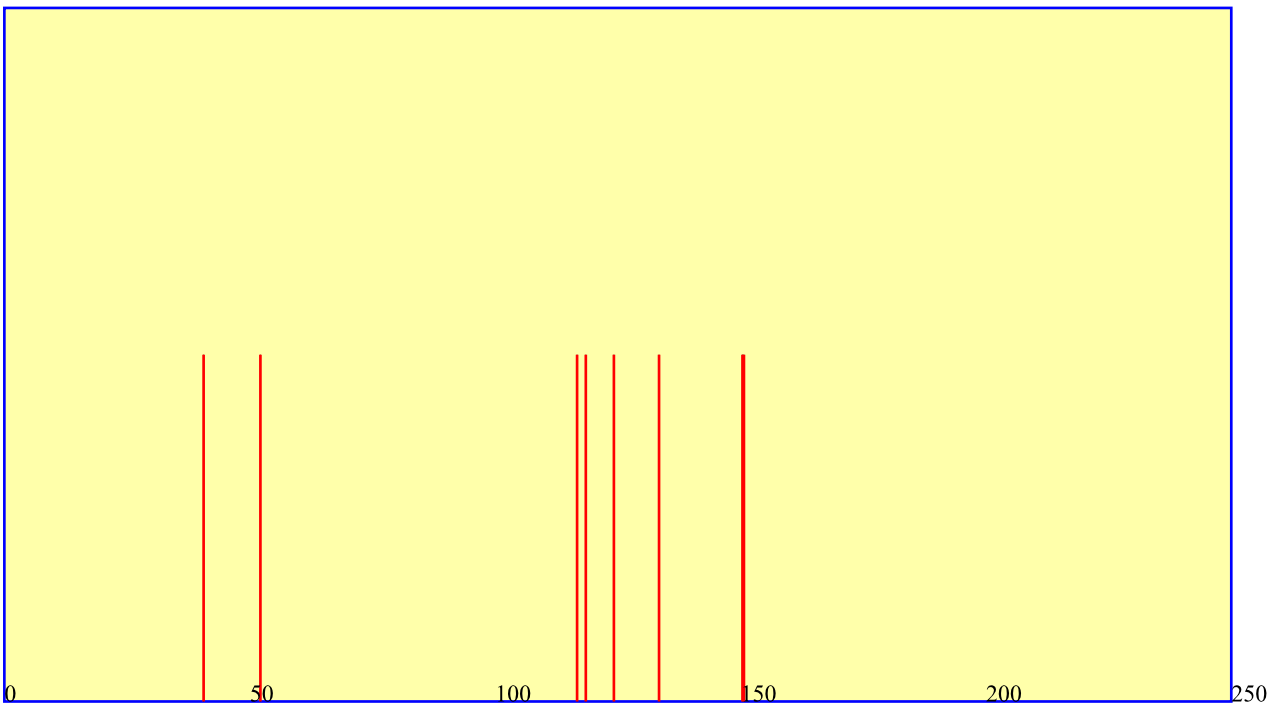
MS: NH [3] *()()*
Found:
Formula:
method:
Required:
overall:

Preparation of (R)-3-(3,4-difluorophenyl)-3-aminopropionic acid(42)

Preparation of (*R*)-3-(3,4-difluorophenyl)-3-aminopropionic acid42CAN (15.0g, 27.42mmol) was added portionwise to a stirred solution of**41**(2.20g, 4.57mmol) in MeCN:H [2] O (150ml, 5:1) at RT. After 16h sat aq NaHCO [3] (100mL) was added. The reaction mixture was partitioned between Et [2] O (3CHAR:18050ml) and H [2] O (100mL) and the solvent removed*in vacuo*. 1MHCl (15ml) was added to the crude reaction mixture and the resultant solution was stirred at RT for 16hours before concentration*in vacuo*. Purification*via*ion exchange chromatography gave**42**(575 mg,63perc) as a white solid; mp 226-230CHAR:730C
OR: [a]D= (*c*,)
HNMR: 500 MHz *(D [2] O)*



CNMR: 125 MHz *(D [2] O)*



MS: APCI {+} *()()*
Found:
Formula:

method:
Required:
overall:

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References