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An Alternative Approach to Aminodiols from Baylis-Hillman Adducts. Stereoselective Synthesis of Chloramphenicol, Fluoramphenicol and Thiamphenicol

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Descrevemos aqui uma nova interpretação para a espectros de banda larga da síntese estereoseletiva de antibióticos de adutos Baylis-Hillman. A estratégia é baseada na preparação de um enocarbamato diretamente do aduto Baylis-Hillman, usando um rearranjo de Curtius. A hidroboração estereoseletiva fornece uma mistura de aminocalcos diasteroisomeros (syn e anti). Após separação cromatográfica, o diasteroisômero syn foi diretamente transformado no antibiótico.

We describe herein a new approach for the stereoselective synthesis of broad spectrum antibiotics from Baylis-Hillman adducts. The strategy is based on the preparation of an ene-carbamate directly from a Baylis-Hillman adduct using a Curtius rearrangement reaction. Stereoselective hydroboration furnished a mixture of diastereoisomeric aminoalcohols (syn and anti). After chromatographic separation, the syn diastereoisomer was directly transformed into the antibiotics.

Keywords: chloramphenicol, Baylis-Hillman, fluoramphenicol, thiamphenicol, α-hydroxy-methylketones

Introduction

The indiscriminate use of antibiotics in the Western World for the treatment of innumerous infectious diseases has caused as a principal consequence, the appearance of several microorganism species with drug multiresistance. One of the most obvious strategies to overcome this problem is the utilization of more potent antibiotics but these can cause undesirable effects to patients. In the last few years some older antibiotics have being reintroduced as therapeutics for the treatment of infections caused by drug-multiresistant microorganisms. Among these antibiotics chloramphenicol and its derivatives appear as interesting alternatives. Due to toxicological problems, these antibiotics were banned from routine usage and their clinical use was restricted to some specific infectious diseases. Recently several papers and patents reported the utilization of chloramphenicol and its derivatives as valuable options for the treatment of some infectious disease with the toxicity of these drugs being under reinvestigation.

Chloramphenicol is the first example of an antibiotic discovered through screening of soil microorganisms and is also the only example of this class of therapeutical compound which was commercialized (Figure 1). There are in the literature numerous papers describing the racemic and asymmetric total syntheses of chloramphenicol and its derivatives, some of them published in the last five years.

![Figure 1. Chloramphenicol (1) and its synthetic derivatives.](image)

1. R= NO₂, X= Cl - Chloramphenicol  
2. R= NO₂, X= F - Fluoramphenicol  
3. R= SO₂CH₃, X= Cl - Thiamphenicol

natural chloramphenicol and also its derivatives have two asymmetric centers with absolute configuration (R,R) and syn relative stereochemistry. Although showing decreased antibiotic properties, the racemic mixture is also biologically active, with the anti diastereoisomer being completely inactive.

Recently our research group reported a strategy to prepare 2-amino-1,3-diols from Baylis-Hillman adducts, which has permitted the synthesis of an oxazolidinone core which exhibited antibiotic properties. An adaptation of this strategy was used recently by us in the synthesis of some substituted tetrahydroisoquinolinones.
Based on a research program focused on the demonstration of the synthetic versatility of Baylis-Hillman adducts as substrates for the synthesis of natural products, we describe herein an alternative approach to directly prepare aminodiols. The stereoselective synthesis of chloramphenicol, fluoramphenicol and thiamphenicol exemplifies the versatility of this strategy.

Results and Discussion

1,2- and 1,3-Aminoalcohol moieties are ubiquitous substructures associated with biologically active natural products. Owing to their biological importance and synthetic relevance, there are in the literature several approaches to prepare them. In a previous communication, we described an approach to prepare 1,3 aminoalcohols, in which the insertion of the nitrogen atom was achieved via a Curtius rearrangement carried out on a derivative obtained from a Baylis-Hillman adduct. Despite the good chemical yields and operational convenience, this sequence was too long. To take advantage of the functionalities exhibited by the Baylis-Hillman adduct, we decided to investigate an alternative, in which the carboxylate group is used directly as substrate for the Curtius rearrangement, as depicted in Scheme 1. This simple modification could improve the synthetic sequence previously described and increased its efficiency.

Based on this retrosynthetic analysis, the antibiotics 1-3 could be prepared from aminoalcohols 4 and 5 by an amidation reaction. These aminoalcohols could potentially be secured by a hydroboration reaction of the ene-carbamates 6 and 7. Ene-carbamates 6 and 7 could be prepared via a Curtius rearrangement followed by the reaction of intermediate vinyl isocyanates with t-butanol. Acrylic acid derivatives could be easily prepared from basic hydrolysis of the Baylis-Hillman adducts 10 and 11.

Depending on the stereoselectivity attained in this sequence, the utilization of an enantiomerically pure Baylis-Hillman adduct could allow the development of an asymmetric version of this strategy. Alternatively, hydroboration could be used as an option to control the relative and absolute stereochemistries of 4 and 5.

Preparation of the Baylis-Hillman adducts and hydrolysis of the ester

Our work was started with the preparation of adducts 10 and 11. Thus, the Baylis-Hillman reaction between methyl acrylate, 4-nitrobenzaldehyde and 4-methylsulfonylbenzaldehyde, in the presence of DABCO and ultrasound, gave the corresponding adducts with 97% and 95% yields, respectively. To achieve these chemical yields different experimental conditions were tested, which are summarized in Table 1.

The use of methyl acrylate as solvent or polar solvents such as acetonitrile furnished better yields as well as a significant decrease in the reaction time. These experimental conditions can be easily scaled up to 10 g or more of aldehyde.

To facilitate the Curtius rearrangement adducts 10 and 11 were treated with tert-butyldimethylsilyl triflate in dichloromethane and triethylamine to give the silylated ethers 12 and 13, in almost quantitative chemical yield (99%). The crude ethers, used without additional purification, were treated with LiOH, in a mixture of acetonitrile: H₂O (1:1) at 40-50 °C, to provide acids 8 and 9, in 96% and 90% yields, respectively (Scheme 2).

The purities obtained for both acids were high enough to allow their direct utilization in the next steps (Scheme 2).

Table 1. Experimental conditions for Baylis-Hillman reactions

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Experimental Condition</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solvents</td>
<td></td>
</tr>
<tr>
<td>4-NO₂Ph</td>
<td>CH₂Cl₂</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>methyl acrylate</td>
<td>9%</td>
</tr>
<tr>
<td>4-CH₃SO₂Ph</td>
<td>CH₂Cl₂/CH₃OH (3:1)</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>CH₂Cl₂/CH₃OH (1:3)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>CH₃CN</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>CH₃CN: methyl acrylate (1:1)</td>
<td>95%</td>
</tr>
</tbody>
</table>

* yields for isolated and purified products.
To insert the nitrogen atom into this structure, a solution of acids 8 and 9 in acetone was treated with ethyl chloroformate and triethylamine for 15 minutes at 0 °C, to give the corresponding anhydrides, which were not isolated. The crude anhydrides were treated with a solution of sodium azide in water (1 g/ 3 mL) at 0 °C for 50 min. After this time, the resulting mixture was refluxed in toluene for 1 h to give the vinyl isocyanates, which in turn were refluxed in methanol. Unfortunately these ene-carbamates 14 and 15 proved to be very unstable to different conditions (acid or base) degrading to a very stable product. A careful analysis of the 1H and 13C NMR spectra showed the formation of the methyl ketones 16 and 17. Most probably this product was formed by hydrolysis of the ene-carbamate followed by an equilibration step to an imine and hydrolysis as depicted in Scheme 3. This represents the first report concerning the preparation of α-hydroxymethyl ketones with the loss of one carbon unit directly from Baylis-Hillman adducts.

To circumvent the high instability of the carbomethyloxy ene-carbamates we decided to intercept the vinyl isocyanates with t-butanol in order to prepare the corresponding tert-butyloxycarbonyl ene-carbamate, which was shown to be much more stable, as expected.

Seeking to increase the efficiency of this sequence, we tried to prepare the ene-carbamates by the direct treatment of acids 8 and 9 with DPPA (diphenyl phosphoryl azide) in toluene under reflux in the presence of triethylamine. Unfortunately, the use of DPPA was unsuccessful although the isomerization through the mixt anhydride proved to be viable.

Preparation of aminoalcohols, determination of relative stereochemistry and synthesis of the antibiotics

The hydroboration reaction of ene-carbamates 6 and 7 was carried out using two different boranes, BH$_3$(S(CH$_3$)$_2$) and 9-BBN. Our intention was to evaluate the degree of diastereoselection, since there is a relationship between the size of the borane and the diastereoselectivity.$^{1}$

Ene-carbamates 6 and 7 were treated separately with BH$_3$(S(CH$_3$)$_2$) and 9-BBN in THF, at 0 °C for 18 h. Then, a 3 mol L$^{-1}$ solution of NaOH and 30% H$_2$O$_2$ was added to the reaction mixture at 0 °C for 2 h to give the corresponding aminoalcohols ($18_{a,b}$/19$_{a,b}$), as a mixture of diastereoisomers, in 65% yield. The results are summarized in Table 2.

The presence of two large substituents directly bonded to the double bond (TBS and Boc) could perhaps explain the poor diastereomeric ratio observed for both boranes. Due to the size of these substituents the approximation of BH$_3$ apparently occurs at both faces, with a discrete preference for the Re face. Otherwise, when the size of the boron reagent was increased we observed a complete loss of diastereoselectivity. To check this alternative, ene-carbamate 6 was treated with TBAF/THF and the resulting alcohol was...
used as substrate for a hydroboration reaction. Unfortunately, no significant change in the diastereoselectivity ratio has been observed (~1.8: 1.0, syn : anti).

The diastereoisomers were readily separated, by conventional silica gel column chromatography. At this stage of the work, the relative configuration of the diastereoisomers should be determined before going on with the strategy. In effect, we had two alternatives to evaluate: determine the relative stereochemistry or finish the total synthesis of the antibiotics and compare our spectral and physico-chemical data with those available in literature. From our point of view the second option was the easier way to finish the synthesis.

The major diastereoisomer 18a was treated with HCl (6 mol L⁻¹) in ethyl acetate (1:1) at room temperature for 3 h to give the corresponding amino alcohol in 98% yield, after purification by ion exchange chromatography.

The results could be rationalized as shown in Figure 2 below.¹⁸

The purified aminoalcohol 4 was then refluxed in methyl dichloroacetate for 3 h to provide the N-acetylated product in 79% yield. All the spectroscopic and physico-chemical data of this compound are completely compatible with those described for a synthetic sample of Chloramphenicol (1). Based on this data the major product obtained in the hydroboration step is that with the relative syn stereochemistry.¹⁸ To finish the synthesis of Fluoramphenicol Table 2.

### Table 2. The hydroboration reaction of ene-carbamates

<table>
<thead>
<tr>
<th>Borane</th>
<th>Carbamate</th>
<th>syn : anti</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH₃.S(CH₃)₂</td>
<td>6</td>
<td>2 : 1</td>
<td>65</td>
</tr>
<tr>
<td>9-BBN</td>
<td>6</td>
<td>1 : 1.2</td>
<td>36</td>
</tr>
<tr>
<td>BH₃.S(CH₃)₂</td>
<td>7</td>
<td>1.5 : 1</td>
<td>65</td>
</tr>
<tr>
<td>9-BBN</td>
<td>7</td>
<td>1 : 1</td>
<td>40</td>
</tr>
</tbody>
</table>

¹ i. borane, THF, 0 °C → r.t.; ii. 3 mol/L NaOH, H₂O₂, 0 °C → r.t.; ∆. the diastereoisomeric ratio was measured by ¹H NMR.

Figure 2. Rationalization to explain the diastereoselectivity observed in the hydroboration reactions.

Scheme 4. Reagents and conditions: a) Ethyl acetate : HCl (6 mol L⁻¹) (1:1), r.t., 3 h, 98%; b) Methyl dichloroacetate, reflux, 3 h, 79%; c) Methyl difluoroacetate, reflux, 4 h, 85%.
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(2), the aminoalcohol 4 was refluxed with methyl difluoroacetate for 4 h to afford 2, in 85% yield (Scheme 4).

The same procedure was repeated with the aminoalcohol 19a, which has been treated with a mixture of ethyl acetate and hydrogen chloride to provide the aminoalcohol 5, in 90% yield, after purification by ion exchange chromatographic. The latter was then refluxed with methyl dichloroacetate to give racemic thiamphenicol (3) as the sole product in 65% yield (Scheme 5). Recently, Wu et al.10 have employed aminoalcohol 5 as the intermediate in the total synthesis of florfenicol, representing a formal synthesis of this antibiotic.

All spectroscopic and physical data of thiamphenicol are completely compatible with those available in the literature and with that of a commercial sample.

Conclusion

We have demonstrated the preparation of some broad spectrum antibiotics from Baylis-Hillman adducts, using a simple and straightforward strategy that can be readily scaled up.20 Chloramphenicol and fluoramphenicol were synthesized in 8 steps with overall yields of 20% and 23%, respectively. Thiamphenicol was also synthesized in 8 steps with an overall chemical yield of 20%.21 As it is possible to obtain enantiomerically pure Baylis-Hilman adduct, this sequence could be used as a valuable alternative for the asymmetric synthesis of these antibiotics.22

The Baylis-Hillman adducts are easily transformed to $\alpha$-hydroxy-methyl ketones in 3 steps with an overall yield up to 74-76%. This generality, as well as the synthetic utility of this method, are under investigation in our laboratory and the results will be described in the due time.

Experimental

The $^1$H and $^{13}$C spectra were recorded on a Varian GEMINI BB-300 at 300 MHz and 75.4 MHz, respectively, or on an Inova instrument at 500 MHz and 125 MHz, respectively. The mass spectra were recorded using a HP model 5988A GC/MS with a High Resolution Autospec-Micromass/EBE. IR were obtained with a Nicolet model Impact 410. Melting points were measured in open capillary tubes using an Electrothermal model 9100 apparatus and are uncorrected. Yields were determined from GC analyses on a HP6890 equipment with a flame ionization detector, using a HP-5 capillary (crosslinked 5% phenylmethylsiloxane, 28 m) column. Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified.

Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All Baylis-Hillman reactions were sonicated in an ultrasonic cleaner UNIQUE model GA 1000 (1000W, 25 kHz). Ice was added occasionally to avoid increasing the temperature of the water bath of the ultrasonic cleaner, which was maintained between 35-40 °C. Reagents were purchased from Aldrich, Acros or Lancaster and were used without purification.

(±)-Methyl 2-{hydroxy(4-nitrophenyl)methyl} acrylate (10)

A mixture of 4-nitrobenzaldehyde (0.75 g, 5 mmol), methyl acrylate (5.16 g, 5.4 mL, 12 eq.) and DABCO (0.36 g, 0.65 eq.) was sonicated for 4 h, at room temperature. After this time, the reaction mixture was diluted with ethyl acetate (10 mL) and the organic phase was washed with water. (±)-Methyl 2-[hydroxy(4-nitrophenyl)methyl] acrylate (10) was obtained as a white solid (5.56 g), 50% yield, m.p. 75-76 °C. The 1H NMR and 13C NMR spectra are in agreement with the reported data.23 The mass spectrum displayed the molecular ion at m/z 283, corresponding to the molecular formula $\text{C}_{17}\text{H}_{18}\text{O}_3\text{N}$.
brine (2 × 20 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate : hexane (70: 30) as eluent to provide 1.15 g (97%) of a lightly yellow viscous oil. IR (KBr) ν max/cm⁻¹: 3078, 2954, 2931, 2858, 2588, 1697, 1523, 1350, 1257, 1088, 872, 837; ¹H NMR [300 MHz, CO(CD₃)₂] δ = 16.2, 23.7, 25.6, 27.5, 72.6, 123.5, 127.1, 127.2, 140.8, 147.3, 148.5, 166.2; HRMS (70 eV , 70 eV, m/z): M⁺ - t-Bu 294.07977; Found M⁺ - t-Bu 294.080140.

(±)-Methyl 2-{[(tert-butyldimethylsilanyloxy)-(4-nitrophenyl)methyl] acrylate (11)

A solution of 4-methanesulfonylbenzaldehyde (0.92 g, 5 mmol) and DABCO (0.36 g, 0.65 eq.) in a mixture of methyl acrylate and acetonitrile (1:1, 20 mL) was sonicated for 2 h at room temperature. After that, the reaction medium was diluted with ethyl acetate (100 mL) and the organic layer was washed with (2 x 20 mL) and finally the organic layer was washed successively with HCl solution (0.5 mol L⁻¹), aqueous solution of NaHCO₃ and brine. The reaction medium was then warmed up to 40-50 °C for 4 h. After that, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate : hexane (5: 95) as eluent to provide 13 (0.38 g, > 99%), as a colorless viscous oil. IR (Film) ν max/cm⁻¹: 3431, 2955, 2936, 2854, 1713, 1647, 1437, 1303, 1248, 1147, 854; ¹H NMR (300 MHz, CDCl₃) δ = -0.096 (s, 3H), 0.044 (s, 3H), 0.86 (s, 9H), 3.02 (s, 3H), 5.68 (s, 1H), 6.32 (s, 1H), 7.55 (d, 2H, J 8.4 Hz), 7.83 (d, 2H, J 8.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = 25.6, 71.9, 123.4, 125.0, 127.7, 142.8, 147.2, 150.2, 165.8; HRMS (70 eV, m/z): M⁺ - t-Bu calc. for C₁₇H₂₅O₅SiN, 326.0644; Found M⁺ - t-Bu 326.0643.

General procedure for the preparation of acids 8 and

To a stirred solution of 11 (0.27 g, 1 mmol) in anhydrous dichloromethane (5 mL), under dry nitrogen atmosphere, was added triethylamine (0.2 g, 0.27 mL, 2.0 mmol) of tert-butylidimethylsilyl trifluoromethanesulfonate (0.32 g, 1.5 mmol), at room temperature. After 4 h, reaction medium was diluted with ethyl acetate (60 mL) and washed successively with HCl solution (0.5 mol L⁻¹), saturated solution of NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄ and evaporated. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate : hexane (5: 95) as eluent to provide 13 (0.38 g, > 99%), as a colorless viscous oil. IR (Film) ν max/cm⁻¹: 3431, 2955, 2936, 2854, 1713, 1647, 1437, 1303, 1248, 1147, 854; ¹H NMR (300 MHz, CDCl₃) δ = -0.096 (s, 3H), 0.044 (s, 3H), 0.86 (s, 9H), 3.02 (s, 3H), 5.68 (s, 1H), 6.32 (s, 1H), 7.55 (d, 2H, J 8.4 Hz), 7.83 (d, 2H, J 8.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = -0.096, 0.043, 0.86 (s, 9H), 25.6, 71.9, 123.4, 125.0, 127.7, 142.8, 147.2, 150.2, 165.8; HRMS (70 eV, m/z): M⁺ - t-Bu calc. for C₁₇H₂₅O₅SiN, 326.0644; Found M⁺ - t-Bu 326.0643.

To a stirred solution of 10 (0.23 g, 1 mmol) in anhydrous dichloromethane (5 mL), under dry nitrogen atmosphere, was added triethylamine (0.2 g, 0.27 mL, 2.0 mmol) and tert-butylidimethylsilyl trifluoromethanesulfonate (0.32 g, 1.5 mmol), at room temperature. After 4 h, reaction medium was diluted with ethyl acetate (60 mL) and washed successively with HCl solution (0.5 mol L⁻¹), saturated solution of NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄ and evaporated. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate : hexane (5: 95) as eluent to provide 13 (0.38 g, > 99%), as a colorless viscous oil. IR (Film) ν max/cm⁻¹: 3431, 2955, 2936, 2854, 1713, 1647, 1437, 1303, 1248, 1147, 854; ¹H NMR (300 MHz, CDCl₃) δ = -0.096 (s, 3H), 0.044 (s, 3H), 0.86 (s, 9H), 3.02 (s, 3H), 5.68 (s, 1H), 6.32 (s, 1H), 7.55 (d, 2H, J 8.4 Hz), 7.83 (d, 2H, J 8.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = -0.096, 0.043, 0.86 (s, 9H), 25.6, 71.9, 123.4, 125.0, 127.7, 142.8, 147.2, 150.2, 165.8; HRMS (70 eV, m/z): M⁺ - t-Bu calc. for C₁₇H₂₅O₅SiN, 326.0644; Found M⁺ - t-Bu 326.0643.
δ -0.02 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 5.80 (s, 1H), 6.18 (s, 1H), 6.35 (s, 1H), 7.70 (d, 2H, J 8.8 Hz), 8.20 (d, 2H, J 8.8 Hz); 13C NMR [75 MHz, CO(CD3)2] δ -0.096 (s, 6H), 0.78 (s, 9H), 2.25 (s, 3H), 2.94 (s, 3H), 5.24 (broad s, 1H), 7.57 (d, 2H, J 8.0 Hz), 7.84 (d, 2H, J 8.0 Hz); 13C NMR (75 MHz, CDCl3) δ -4.76, 18.4, 21.7, 26.0, 44.6, 91.3, 122.4, 126.3, 137.6, 142.1, 211.5 (C); HRMS (70 eV, m/z): M+ calc. for C16H23NO4Si 309.13954; Found M+ 309.13954.

General procedure for the preparation of ene-carbamates 6 and 7

To stirred solutions of acids 8 or 9 (1 mmol) in 10 mL of acetone, at 0 °C, were added anhydrous triethylamine (0.20 g, 0.26 mL, 2 eq.) and ethyl chloroformate (0.16 g, 0.143 mL, 1.5 eq.). The resulting solution was stirred for 15 minutes at 0 °C, followed by the addition of a solution of sodium azide (0.1 g) in water (0.3 mL). After 1 h at 0 °C, the reaction mixture was diluted with dichloromethane (30 mL) and the organic layer was washed with distilled water (10 mL), brine (10 mL), dried over anhydrous Na2SO4, and the solvent was evaporated under reduced pressure. Then, the oily residue was refluxed in anhydrous toluene (10 mL) for 1 h. After this time, the solvent was removed under reduced pressure and the residue was refluxed in water (10 mL) for 2 h. The reaction mixture was then diluted with dichloromethane (40 mL) and the organic phase was washed with brine (10 mL), dried over anhydrous Na2SO4, and the solvent was evaporated. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate : hexane (5:95) as eluent to give the corresponding ene-carbamates.

1-{[(tert-Butyldimethylsilanyloxy)-(4-nitrophenyl)-methanesulfonyl phenyl]-propan-2-one (17). 0.273 g, 80% overall yield; IR (Film) ν max/cm−1: 2954, 2929, 2859, 1720, 1523, 1345, 1257, 1084, 836, 544; 1H NMR (300 MHz, CDCl3) δ -0.096 (s, 6H), 0.78 (s, 9H), 2.25 (s, 3H), 2.94 (s, 3H), 5.24 (broad s, 1H), 7.57 (d, 2H, J 8.0 Hz), 7.84 (d, 2H, J 8.0 Hz); 13C NMR (75 MHz, CDCl3) δ -4.76, 18.4, 21.7, 26.0, 44.6, 91.3, 122.4, 126.3, 137.6, 142.1, 211.5 (C); HRMS (70 eV, m/z): M+ calc. for C16H23NO4Si 342.13211; Found M+ 342.13209.
1H), 5.54 (s, 1H), 6.88 (s, 1H), exchangeable with D2O), 7.75 (d, 2H, J 8.8 Hz), 7.92 (d, 2H, J 8.8 Hz); 13C NMR [75 MHz, CO(CD3)2] δ -5.5 (CH3), -5.4 (CH3), 18.2 (3 x CH3), 24.4 (3 x CH3), 27.9, 44.6, 47.9, 71.7, 79.1, 95.6, 122.9, 126.1, 141.9, 147.5, 151.7, 152.8; Calc. for C21H35NO3SSi C 57.11 H 7.99%; Found C 57.09 H 7.98%.

General procedure for the preparation of aminoalcohols 18a/b and 19a/b

To stirred solutions of ene carbamates 6 or 7 (1 mmol) in THF (8 mL), at 0 °C, under nitrogen atmosphere, was slowly added a solution of BH2,SH(CH3)2 (5 mL, conc. 1 mol L-1) in THF). After the addition of the borane solution, the reaction medium was warmed to room temperature and stirred for 16 h. After that, the temperature of the resulting solution was lowered to 0 °C. Then, a solution of NaOH (5 mL, conc. 3 mol L-1) was added, followed by the careful addition (drop by drop) of 30% H2O2 (5 mL). The mixture was stirred for 45 minutes at 0 °C and for 45 minutes more at room temperature. After this time, a saturated solution of NaHCO3 (20 mL), distilled water (20 mL) and brine (20 mL) was added and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with saturated solution of NaHCO3 (20 mL), distilled water (20 mL) and dried over Na2SO4. The solvent was removed under reduced pressure. The diastereoisomers were separated by silica gel column chromatography using a mixture of ethyl acetate : hexane (30 : 70) as eluent.

HRMS (70 eV, m/z): M+ calc. for C20H34N2O6Si 426.21862; M+ Found 459.21100.

(±)-2-Syn-[2-(tert-Butyldimethylsilanyloxy)-1-hydroxymethyl-2-(4-nitrophenyl)-ethyl]-carboxylic acid t-buty1 ester (19a). 0.12 g, 65% overall yield; IR (Film) νmax/cm-1: 3383, 3251, 2956, 2854, 1688, 1347, 1085, 838, 793; 1H NMR [300 MHz, CDCl3] δ -0.12 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.27 (s, 9H), 3.62 (m, 2H), 3.75 (m, 2H), 3.83 (m, 2H), 3.83 (m, 1H), 5.07 (m, 1H), 6.77 (m, 2H), 7.69 (d, 2H, J 7.3 Hz), 8.22 (d, 2H, J 8.8 Hz); 13C NMR [75 MHz, CDCl3] δ 5.07, 5.07, 12.4, 12.4, 25.8, 25.8, 44.5, 44.5, 58.3, 71.7, 71.7, 139.5, 139.5, 147.6, 147.6; Calc. for C19H33NO3Si, M+ calc. for C19H33NO3Si 459.21109; M+ Found 459.21100.

General procedure for the preparation of aminodiols and 5

To stirred solutions of the syn diastereoisomers 18 or 19a (0.2 mmol) in 4 mL of ethyl acetate, at room temperature, was added a solution of hydrochloric acid (4 mL, conc. 6 mol L-1). After 3 h, the resulting solution was extracted twice with ethyl ether (30 mL) and the ether phase was separated. The temperature of the aqueous layer was lowered to 0 °C and the pH was adjusted to 7-8 with solid NaHCO3. The slightly basic aqueous phase was successively extracted with ethyl acetate (5 x 30 mL). The organic phases were combined and dried on anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by exchange chromatography column on Dowex.
122.6, 142.9, 147.4; Calc. for C₉H₁₂N₂O₄ C 59.94, H 5.70%;
Found C 59.92, H 5.70%.

Synthesis of (±)-chloramphenicol (1)

A stirred solution of aminodiol 4 (0.04 g, 0.2 mmol) in methyl dichloroacetate (10 mL) was refluxed for 3 h. After that time, the temperature of the reaction solution was lowered to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using a mixture of acetone : ethyl acetate (10:90) to provide (±)-chloramphenicol (1) as a white solid (0.024 g, 85%), m.p. 164-165 °C; IR (KBr) ν max/cm⁻¹: 3787, 2924, 2859, 1690, 1518, 1349, 1070, 851; 1H NMR [500 MHz, CO(CD₃)₂] δ 3.21 (m, 1H), 3.30 (m, 1H), 3.32 (s, 3H), 3.97 (m, 2H), 4.59 (d, J 9.3Hz, 2H); 13C NMR [75 MHz, CO(CD₃)₂] δ 39.3, 54.6, 63.8, 75.1, 122.4, 122.8, 135.7, 143.9; Calc. for C₁₀H₁₅NO₄S C 66.0, 118.5, 122.8, 146.0, 159.2; HRMS (70 eV, m/z): M⁺ Calc. for C₁₀H₁₅Cl₂N₂O₅ 355.00480; Found 355.00455.

Synthesis of (±)-fluoramphenicol (2)

A stirred solution of aminodiol 4 (0.02 g, 0.1 mmol) in methyl difluoroacetate (5 mL) was refluxed for 3 h. After that time, the temperature of the reaction solution was lowered to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using a mixture of acetone : ethyl acetate (10:90) to provide (±)-fluoramphenicol (2) as a white solid (0.024 g, 65%), m.p. 164-166.5 °C; IR (KBr) ν max/cm⁻¹: 3787, 2924, 2859, 1690, 1518, 1349, 1070, 851; 1H NMR [500 MHz, CO(CD₃)₂] δ 3.17 (m, 1H), 3.30 (m, 1H), 3.47 (s, 3H), 3.76 (m, 2H), 4.07 (m, 1H), 5.31 (s, 1H), 6.21 (s, 1H), 6.39 (s, 1H), 7.56 (m, 1H), 7.70 (d, 2H), 7.85 (d, 2H); 13C NMR [75 MHz, CO(CD₃)₂] δ 39.3, 52.7, 56.9, 62.3, 66.1, 118.5, 122.8, 142.7, 146.0, 159.2; HRMS (70 eV, m/z): M⁺ Calc. for C₁₁H₁₅F₂N₂O₅S 370.07134; Found 370.07139.

Synthesis of (±)-thiophenamphenicol (3)

A stirred solution of aminodiol 5 (0.025 g, 0.1 mmol) in methyl dichloroacetate (5 mL) was refluxed for 1 h. After that time, the temperature of the reaction solution was lowered to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography using a mixture of acetone : ethyl acetate (10:90) to provide (±)-thiophenamphenicol (3) as a white solid (0.024 g, 65%), m.p. 164-166.5 °C; IR (KBr) ν max/cm⁻¹: 3787, 2924, 2859, 1690, 1518, 1349, 1070, 851; 1H NMR [500 MHz, CO(CD₃)₂] δ 3.04 (m, 1H), 3.30 (m, 1H), 3.47 (s, 3H), 3.76 (m, 2H), 4.07 (m, 1H), 5.31 (s, 1H), 6.21 (s, 1H), 6.39 (s, 1H), 7.56 (m, 1H), 7.70 (d, 2H), 7.85 (d, 2H); 13C NMR [75 MHz, CO(CD₃)₂] δ 39.3, 52.7, 56.9, 62.3, 66.1, 118.5, 122.8, 142.7, 146.0, 159.2; HRMS (70 eV, m/z): M⁺ Calc. for C₁₁H₁₅Cl₂N₂O₅S 370.07134; Found 370.07139.

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References


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