Article

Diastereoselective Synthesis of Substituted 2-Amino-1,3-propanediols from Morita-Baylis-Hillman Adducts

Paulo H. S. Paioti, Patrícia Rezende and Fernando Coelho*

Laboratório de Síntese de Produtos Naturais e Fármacos, Instituto de Química,
Universidade Estadual de Campinas, CP 6154, 13083-970 Campinas-SP, Brazil

Descrevemos nesse artigo uma abordagem diastereosseletiva, a partir de adutos de Morita-Baylis-Hillman (MBH), para a preparação de sistemas 2-amino-1,3-propanodióis substituídos com estereoquímica relativa *anti*. Estas unidades estruturais têm sido utilizadas como intermediárias para a síntese de diversas substâncias de interesse farmacológico e comercial. Nessa estratégia, os *anti* 2-amino-1,3-propanodióis foram facilmente preparados por ozonólise de dióis alílicos obtidos de adutos de MBH, seguido de uma aminação redutiva diastereosseletiva dos 2-oxo-1,3-propanodióis. Para demonstrar a utilidade desses aminodióis, eles foram transformados em oxazolidin-2-onas substituídas, que também foram utilizadas na determinação indireta da configuração relativa dos aminodióis.

We report herein a new diastereoselective approach to substituted 2-amino-1,3-propanediols with *anti* relative stereochemistry from Morita-Baylis-Hillman (MBH) adducts. These structural moieties have been used as intermediates for the synthesis of several compounds with relevant pharmacological and commercial interest. In this strategy, substituted *anti* 2-amino-1,3-propanediols were readily prepared via ozonolysis of allylic diols obtained from MBH adducts, followed by a diastereoselective reductive amination of the substituted 2-oxo-1,3-propanediols. To demonstrate the synthetic utility of these aminodiols, they were transformed into substituted oxazolidin-2-ones, which were also used in the indirect determination of the relative stereochemistry of the aminodiols.

Keywords: 2-amino-1,3-propanediol, Morita-Baylis-Hillman, reductive amination

Introduction

Substituted 2-amino-1,3-propanediols are important structural motifs present in many pharmacologically active compounds, such as antibiotics (*e.g.*, chloramphenicol, fluoramphenicol and its analogues),[1,2] glycosidase inhibitors[3] and sphingolipids[4] (Figure 1).

2-Amino-1,3-propanediols also play an important role as key intermediates in the synthesis of oxazolidin-2-one, which can present not only antibacterial activity, but also increased synthetic applicability.[5] Owing to this fact, there are several reports[6] related to different approaches for the preparation of substituted 2-amino-1,3-propanediols.

In the last years, our group has been working on the preparation of valuable synthetic intermediates by exploring the potentiality of the Morita-Baylis-Hillman (MBH) reaction.[7,8] In this context, our group has previously described the synthesis of chloramphenicol and derivatives

as well as the preparation of substituted 2-quinolinones having *syn* 2-amino-1,3-propanediols in their structures, taking MBH adducts as substrates.[9]

The biological and commercial importance of this structural motif calls for the availability of as many as possible alternative methods to prepare these key compounds. Thus, it is described herein a diastereoselective approach to substituted *anti* 2-amino-1,3-propanediols starting from the MBH reaction. These *anti*-aminodiols have an endothelial differentiation gene (EDG) antagonism. This class of compounds competes with the EDG receptors and can be potentially used for the treatment of circulatory system diseases, such as arteriosclerosis, heat diseases and peripheral circulatory disorders. They can be also used against rheumatism, cancers, diabetes retinopathy, respiratory system diseases and twitch after subarachnoidal hemorrhage.[10]

Our approach is based on a diastereoselective reductive amination of the 2-oxo-1,3-propanediol derivatives (**9-11**), that are easily prepared from double bond ozonolysis
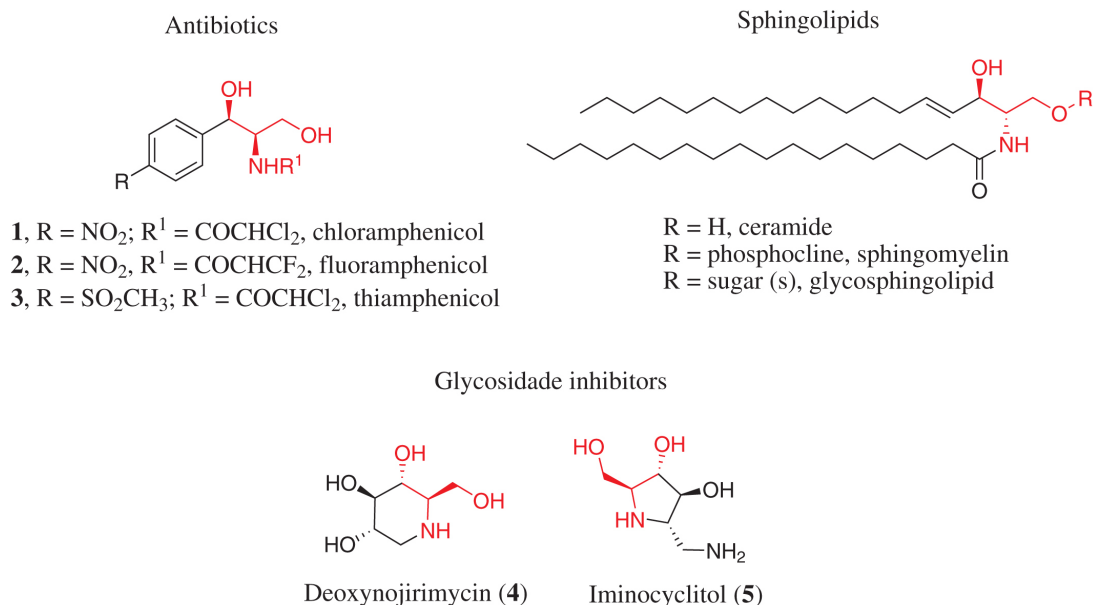
*e-mail: coelho@iqm.unicamp.br

Antibiotics

Sphingolipids

1, R = NO$_2$; R^1 = COCHCl$_2$, chloramphenicol
2, R = NO$_2$, R^1 = COCHCF$_2$, fluoramphenicol
3, R = SO$_2$CH$_3$; R^1 = COCHCl$_2$, thiamphenicol

R = H, ceramide
R = phosphocline, sphingomyelin
R = sugar (s), glycosphingolipid

Glycosidade inhibitors

Deoxynojirimycin (**4**)   Iminocyclitol (**5**)

Figure 1. Biologically active compounds having 2-amino-1,3-propanediol motifs in their structures.

of an allylic diol. The latter is promptly prepared by chemoselective ester reduction of Morita-Baylis-Hillman adducts (**12**-**14**) after silylation of the secondary hydroxyl group. The retrosynthetic analysis is depicted below (Scheme 1).

The relative stereochemistry of our aminodiols is expected to be controlled during the reductive amination step of the oxo-diols (**9**-**11**). Most probably, this control could be exerted by the presence of a ligand with chelating properties in α position, based on the Cram-chelate model of 1,2-induction. This chelation should force the deliverance of the hydride to the less hindered face, as previously reported in other papers from our laboratory.[11]

In this work, it is disclosed a facile and straightforward strategy for the diastereoselective synthesis of 2-amino-1,3-diols from Morita-Baylis-Hillman adducts. Additionally, it is described a regioselective total synthesis of (±)-*trans*-isocytoxazone, an important anti-asthmatic oxazolidin-2-one. Isocytoxazone is an isomer of the natural product cytoxazone, isolated from *Streptomyces sp* yeasts. The biological relevance of both compounds has inspired several approaches to their racemic and asymmetric total

synthesis.[12] Some others 4-substituted oxazolidinones were also synthesized using the strategy disclosed herein.

Results and Discussion

To start our work, it was prepared the MBH adducts (**12**-**14**, for experimental details see Supplementary Information). This was accomplished using our well-established methodology described some years ago (Scheme 2).[13] In the sequence, the MBH secondary hydroxyl group was silylated to afford the protected MBH adducts (**15**-**17**) in good yields. Finally, silylated adducts **15**-**17** were chemoselectively reduced in the presence of DIBAL-H (diisobutylaluminium hydride) at −72 °C, to afford the allylic diols **18**-**20**, in overall yields ranging from 67 up to 72% (Scheme 2).

Silylation was closely related to the reduction and ozonolysis steps. Previous attempts to conduct the ester reduction with the unprotected adducts have required the addition of an excess of DIBAL-H and gave the required allylic diols in low yields (*ca.* 50%). When ozonolysis is performed with silylated adducts, the yields are higher,


6, R = H
7, R = OMe
8, R = NO$_2$

9, R = H
10, R = OMe
11, R = NO$_2$

12, R = H
13, R = OMe
14, R = NO$_2$
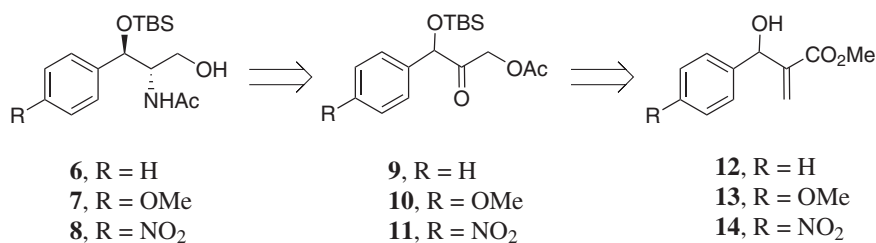
Scheme 1. Retrosynthetic analysis for the preparation of *anti* 2-amino-1,3-propanediols
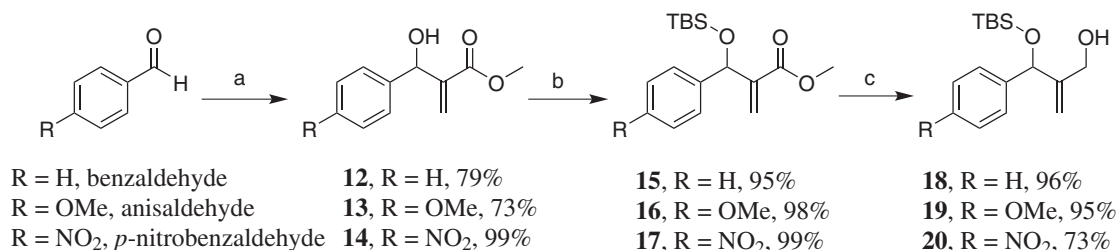
Scheme 2. Preparation of allylic diols from MBH adducts. Reagents and conditions: (a) methyl acrylate, DABCO, room temperature, ultrasound and (b) TBSCl (*tert*-butyldimethylsilyl chloride), imidazole, DMF or TBSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate), CH$_2$Cl$_2$, Et$_3$N and (c) DIBAL-H, CH$_2$Cl$_2$, −72 °C, 1 h.

Table 1. Synthesis of 2-oxo-1,3-propanediols from MBH adducts
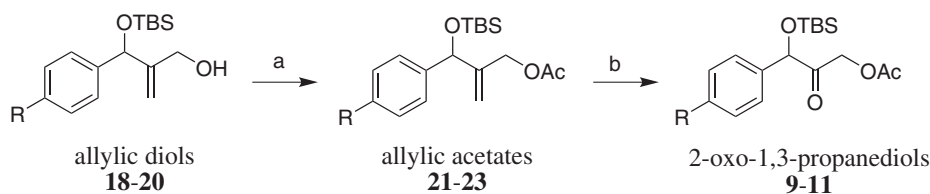
entry	R	Acetylation / %[a]	Ozonolysis / %[a]	Overall yields / %[b]
1	H	**21**, 85	**9**, 91	55
2	OMe	**22**, 90	**10**, 80	49
3	NO$_2$	**23**, 90	**11**, 82	53

Reagents and conditions: (a) AcCl, NEt$_3$, CH$_2$Cl$_2$, 0 °C, 30 min and (b) (*i*) O$_3$, MeOH, −72 °C, 15 min and (*ii*) S(CH$_3$)$_2$, −72 °C to room temperature, 1 h; [a]yields refer to isolated and purified products; [b]yield over 5 steps.

the products are more stable and the purification by usual chromatographic protocols becomes easier. For all these reasons, silylation increases the synthetic efficiency of this sequence since no purification steps are formally needed after ester reduction with DIBAL-H. Finally, diols **18**-**20** were acetylated to provide the corresponding acetates **21**-**23** in good yields (Table 1).

At first, one goal of this work was the selective access to oxazolidin-2-ones with different substitution patterns. To accomplish this task, it would be necessary to be able to remove selectively the protecting groups from the benzylic and primary hydroxyl groups. Thus, acetylation was used as an orthogonal protection of the primary hydroxyl. Acetates **21**-**23** were treated with ozone, at −72 °C, in methanol for 15 min, followed by reductive work-up [S(CH$_3$)$_2$] to give substituted 2-oxo-1,3-propanediols **9**-**11**, with yields ranging from 80 up to 91%.[14] The oxo-derivatives **9**-**11** were therefore prepared in 5 steps from the corresponding aldehydes with good overall yields (Table 1).

Following our synthetic strategy, the oxo-compounds **9**-**11** were then submitted to a reductive amination step. In the literature, it is possible to find several alternatives to perform a reductive amination reaction.[15]

In our case, the reductive aminations were performed in methanol as a solvent, at room temperature, using NH$_4$OAc

as nitrogen source in the presence of NaHCO$_3$. The latter was used to maintain the pH of the reaction under control (pH ranging from 4.5 to 6).

Interestingly, during the reductive amination, it was observed the migration of the acetyl group from oxygen to the newly incorporated nitrogen atom, leading to the formation of 2-*N*-acetyl-1,3-propanediol. This sort of internal migration is widely known,[16] mainly in the aminosugar chemistry.[17]

It was decided to use NaBH$_3$CN as a source of hydride, even though it can reduce carbonyl groups at pH lower than 4.[18] However, such side reactions were avoided since the pH was always maintained above 4 (ranging from 4.5 up to 6). Thus, in these conditions, oxo-compounds **9**-**11** afford the corresponding 2-*N*-acetyl-1,3-propanediols in moderate yields, as shown in Table 2.

Fortunately, the major component present in the crude mixture of the aminopropanediols **6a/b**-**8a/b** crystallizes from a mixture of ethyl acetate and hexane. Surprisingly, the analysis of the NMR (nuclear magnetic resonance) spectra of the crystallized product showed the presence of a single compound. The analysis of these spectra showed a doublet centered around 5.20 ppm attributed to the carbinolic proton.

The products were fully characterized by the usual spectroscopic methods. The analysis of IR (infrared) spectra of the compounds **6a**-**8a** showed a strong absorption near

Table 2. Diastereoselective synthesis of substituted *anti* 2-*N*-acetyl-1,3-propanediols
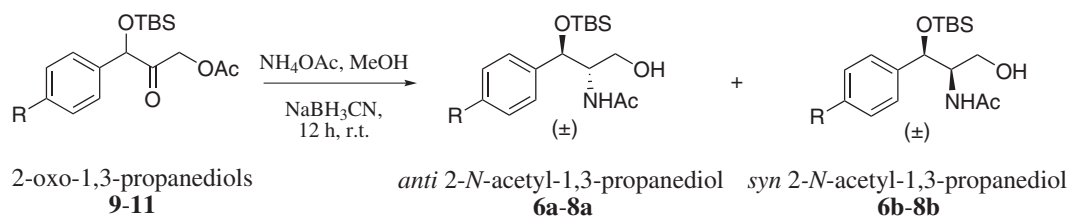
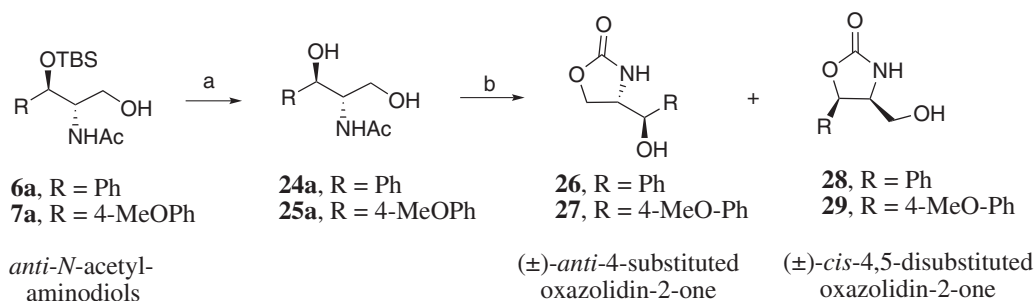| entry	R	Aminodiols / %[a]	Diastereoselectivity (*anti:syn*)[b]
1	**9**, H	**6a**, 52; **6b**, 8	87:13
2	**10**, OMe	**7a**, 53; **7b**, 14	79:21
3	**11**, NO$_2$	**8a**, 40; **8b**, 15	72:28

Reagents and conditions: (a) NH$_4$OAc, NaBH$_3$CN, NaHCO$_3$, MeOH, room temperature, 12 h; [a]yields refer to isolated and purified compounds; [b]diastereoselectivities were determined in the crude mixture by measuring the relative proportion between the signals at 5.2-4.95 ppm, attributed to the carbinolic protons.

to 1650 cm^{-1}, which was assigned to the amide carbonyl group. Furthermore, the analysis of the ^{1}H NMR spectra for all nitrogenated compounds showed a characteristic doublet at 6.50 ppm attributed to the secondary amide hydrogen and a second doublet (ranging from 5.14 to 5.29 ppm) attributed to the carbinolic proton. The analysis of the ^{13}C NMR spectra of these compounds shows signals around 75, 61 and 55 ppm, which were attributed to the secondary and primary carbinolic carbons and to the carbon bonded to the nitrogen, respectively.

Seeking to demonstrate the synthetic versatility of our aminodiols, they were transformed into the corresponding substituted oxazolidin-2-ones. Besides the biological relevance of these cyclic intermediates, they could be subjected to nOe (nuclear Overhauser effect) experiments to confirm the relative stereochemistry. They could be compared with some oxazolidin-2-ones whose relative stereochemistries are already well established. Initially, the interest was in having the 4,5-disubstituted oxazolidin-2-ones. Then, the *anti*-2-*N*-acetyl-1,3-propanediols **6a-7a**

were treated with TBAF (tetrabutylammonium fluoride) in THF (tetrahydrofuran) (at room temperature for 1 h) in order to remove the silyl protecting group. The corresponding unprotected 2-*N*-acetyl-1,3-propanediols were obtained in almost quantitative yield, but were contaminated with a tiny amount of TBAF residue. Attempts to purify the compound **25a** by silica gel column chromatography significantly reduced the yield. The compounds **24a** and **25a** were therefore used in the next step without purification.

The literature reports several methods for preparing oxazolidin-2-one from aminodiols.[19] In our case, the 2-*N*-acetyl-1,3-propanediols **24a** and **25a** were refluxed separately in toluene in the presence of diethylcarbonate and K$_2$CO$_3$ for 1 h. After that, the crude mixture was evaporated and redissolved in a methanol:water (1:1) mixture, which was refluxed in the presence of LiOH to complete the cyclization process. Under such conditions, it was recovered a mixture of 4- and 4-5-substituted oxazolidin-2-ones in moderate yields. The results are summarized in Table 3.

Table 3. Synthesis of oxazolidin-2-ones from aminodiols

6a, R = Ph
7a, R = 4-MeOPh

anti-N-acetyl-aminodiols

24a, R = Ph
25a, R = 4-MeOPh

26, R = Ph
27, R = 4-MeO-Ph

(±)-*anti*-4-substituted oxazolidin-2-one

28, R = Ph
29, R = 4-MeO-Ph

(±)-*cis*-4,5-disubstituted oxazolidin-2-one

entry	Aminodiols	Oxazolidin-2-ones / %[a]	Regioisomeric ratio (4-/4,5-)
1	**6a**	**26**, 33; **28**, 17	2:1[b]
2	**7a**	**27**, 51	> 10:1

Reagents and conditions: (a) TBAF, MeOH, room temperature, 1 h and (b) (*i*) CO(OEt)$_2$, toluene, reflux, K$_2$CO$_3$ and (*ii*) LiOH, MeOH:H$_2$O (1:1), 1 h; [a]yields for purified and isolated oxazolidinones; [b]regioisomers were separated by preparative thin layer chromatography.

In both cases, the formation of 4-substituted oxazolidin-2-ones (**26** and **27**) was favorable, however, when R = Ph (**24a**), a considerable amount of regioisomeric 4,5-substituted oxazolidin-2-one was formed (**28**). Most likely a steric effect associated with the 4,5-substituted *cis* oxazolidin-2-ones leads to the formation of the more stable 4-substituted *anti* oxazolidinones.

The purified minor *syn* 2-amino-1,3-propanediol (**25b**) was also treated with the same cyclization conditions to provide *trans*-isocytoxazone (**30**), contaminated with traces of the regioisomeric 4-substituted oxazolidin-2-one (> 5%). Similar results were previously reported by Rozwadowska *et al.*[12] (Scheme 3).

Our spectral data were compared to those available in the literature for (±)-*trans*-isocytoxazone (**30**) and confirm that our synthesis was successfully accomplished.[12] In order to collect more evidence about this compound, it was also performed some nOe studies. Thus, when the benzylic hydrogen at 5.20 ppm was irradiated, it was observed an increment of only 0.7%, compatible with a 1,2-*trans* relationship.[20] The same protocol was used for the other 4-substituted oxazolidin-2-one (**26**) and **27**. The irradiation of benzylic hydrogen at 4.6/4.7ppm showed increments of 1.4 and 1.5%, respectively. These results suggest, in both cases, an *anti* relationship between the groups[21] (Figure 2).

The *anti* diastereoisomers could be rationalized from the model of 1,2-induction proposed by Cram and Felkin[22] for the reduction of ketones and imines. In this model, not only steric hindrance is considered, but also important electronic effects that can influence the transition state energy. The observed selectivity can be inferred through the formation of a chelate species envolving to the formation of a hydrogen bond between one of the hydrogens of the iminium ion and the oxygen atom of the silyl ether. Molecular orbital studies of different types of silyl ethers showed that oxygen can present chelating properties,[23] supporting the transition state proposed for this imine reduction. The *anti* diastereoisomers can be called anti-Felkin or Cram-chelate product (Figure 3).
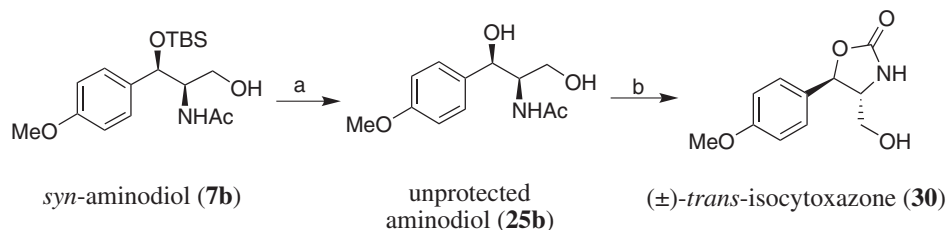
Scheme 3. Synthesis of (±)-*trans*-isocytoxazone. Reagents and conditions: (a) TBAF, THF, 1 h, room temperature and (b) (*i*) CO(OEt)$_2$, K$_2$CO$_3$, toluene, reflux, 1 h and (*ii*) LiOH, MeOH, H$_2$O, 1 h, room temperature, 45% (regioisomeric ratio > 10:1).
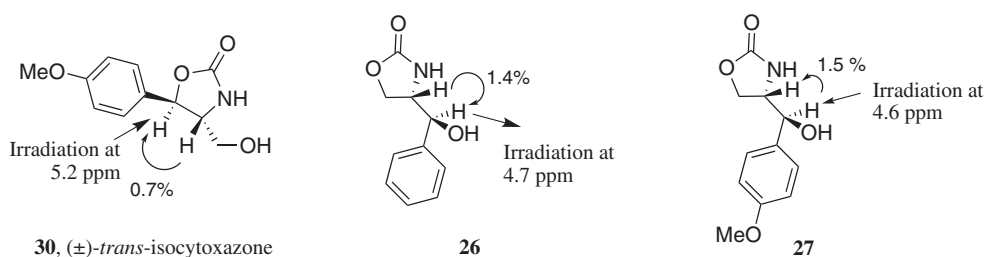

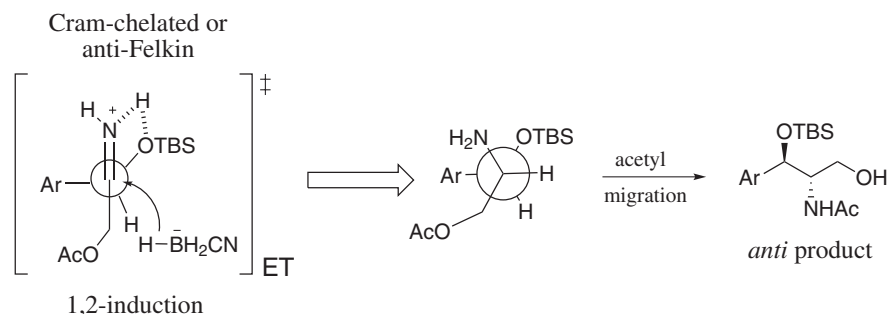Figure 2. nOe differencial studies with the synthesized oxazolidin-2-ones.

Figure 3. Models of 1,2-induction through Cram-chelate or anti-Felkin processes to explain the reduction of the imine group.

Conclusions

In summary, it is described in this work an alternative for the diastereoselective synthesis of *anti* 2-*N*-acetyl-1,3-propanediols from MBH adducts in 5 steps, with overall yields ranging from 25 to 42%. Furthermore, from the *anti*-aminoalcohols **6a** and **7a** regioisomeric 4-substituted oxazolidin-2-ones **26** and **27** were obtained as the major products in 2 steps, in moderate overall yields. It is also described an alternative approach to the total synthesis of (±)-*trans*-isocytoxazone, a synthetic oxazolidino-2-one presenting anti-asthmatic properties. This compound was synthetized from the minor *syn*-aminoalcohol **7b** with yield of 45% over to 2 steps. This is the first report describing the total synthesis of it from Morita-Baylis-Hillman adducts.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini BB-300 at 300 and 75.5 MHz, Bruker 250 at 250 and 62.5 MHz and on an Inova instrument at 500 and 125 MHz, respectively. The mass spectra (MS) were recorded using a Micromass (Manchester-UK) ESI-QqTOF (electrospray ionization quadrupole time-of-flight) with high resolution on the TOF mass analyzer and using a Premier-Waters GC/MS GCT EI-TOF, also with high resolution. Infrared (IR) spectra were obtained with a Nicolet model Impact 410. Melting points (m.p.) were measured in open capillary tubes using an Electrothermal model 9100 apparatus and were not calibrated. 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 (thin layer chromatography) visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All Morita-Baylis-Hillman reactions were sonicated in an ultrasonic cleaner UNIQUE model GA 1000 (1000 W, 25 kHz). Reagents were purchased from Aldrich, Acros, Synth or Merck and were used without purification.

General procedure for the preparation allylic diols (18-20)

To a stirred solution of the silylated MBH adduct **15**-**17** (5 mmol) in 20 mL of anhydrous dichloromethane at −72 °C, it was added quickly (under an inert gas atmosphere) a solution of DIBAL-H in toluene (1.5 mol L^{-1}, 10.4 mL, 12.5 mmol). Soon after, there was the vigorous release of small bubbles, followed by a change of color of the reaction medium. After 1 h, the analysis by TLC revealed the complete consumption of the starting material. Then, a saturated solution of sodium acetate (7 mL) was carefully added to the reaction flask. The resulting mixture was transferred to an erlenmeyer (200 mL) containing 80 mL of ethyl ether. To the stirred mixture, it was added a saturated solution of NH$_4$Cl (12 mL) and the mixture was then stirred for 1 h until the observation of the precipitation of a white gel. After that, the heterogeneous mixture was filtered in a pad of celite (0.5 cm) under vacuum, and the precipitate was washed with ethyl ether (3 × 10 mL). The organic layers were combined and washed with 15 mL of distilled water and 15 mL of brine, dried over MgSO$_4$ and filtered. The organic solvent was removed under reduced pressure. The crude residue was used in the next step without any purification.

General procedure for the preparation of acetylated compounds (21-23)

To a stirred solution of allyl alcohol **18**-**20** (2 mmol) in 15 mL of anhydrous dichloromethane at 0 °C (under an inert gas atmosphere), it was added NEt$_3$ (4 mmol) and freshly distilled acetyl chloride (3 mmol). The reaction was followed by TLC and after 30 min no starting material was detected. Then, a saturated solution of NaHCO$_3$ (10 mL) was added to the reaction mixture. The organic layer was separated and washed with brine (2 × 10 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography, using a mixture of ethyl acetate:hexane (20:80), as eluent, to give the corresponding acetates as viscous oils.

General procedure for the preparation of oxo-derivatives (9-11)

Into a stirred solution of the acetylated compounds **21**-**23** (1 mmol) in 10 mL of methanol (at −72 °C), it was passed a slow flow of ozone. The reaction was followed by TLC until no starting material was detected. After 15 min, dimethyl sulfide was added [S(CH$_3$)$_2$, 10 mmol] and the mixture was stirred at −72 °C for 1 h. Soon after, the solvents were removed under reduced pressure and the residue was diluted in ethyl acetate (30 mL). The organic layer was washed with brine (2 × 20 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography using a mixture of ethyl acetate:hexane (5:95) to provide the corresponding oxo-compounds as fluid oils.

General procedure for the preparation of aminodiols (6-8)

To a stirred solution of substituted 2-oxo-1,3-propanediols **9**-**11** (1 mmol) in 15 mL of anhydrous methanol (under an

inert gas atmosphere), it was added NaHCO$_3$ (2 mmol) and NH$_4$OAc (30 equiv.). To the resulting mixture, it was added NaBH$_3$CN (1.5 equiv.) in two portions (0.75 equiv. each) in intervals of 30 min. The reaction was maintained under stirring for 12 h. After that, the solvent was removed under reduced pressure and the crude residue was suspended in ethyl acetate (20 mL). The organic phase was washed with distilled water (2 × 10 mL), brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to furnish an amorphous solid. This solid was crystallized as following: the crude residue was dissolved in ethyl acetate (the minimum amount necessary to dissolve the product) at 50 °C. Then, the resulting hot solution was transferred to a 100 mL erlenmeyer and hexane was added drop by drop until the solution becomes cloudy. The solution was kept in the refrigerator at 8 °C for 1 day. Then, the precipitate was filtered, washed with 20 mL of cold hexane to provide the *anti* diastereoisomer, as an amorphous solid (0.168 g) and the *syn* diastereoisomer as a viscous oil (0.028 g).

General procedure for the deprotection of the TBS group

To a stirred solution of the *anti* 2-*N*-acetyl-1,3-propanediols **6a-7a** (0.5 mmol) in 10 mL of anhydrous THF at 0 °C (under an inert gas atmosphere), it was added drop by drop a solution of TBAF (1.0 mol L^{-1} in THF, 1.25 mL, 1.25 mmol). The reaction was followed by TLC and after 1 h no starting material was observed. Then, the solvent was evaporated under reduced pressure and the crude residue was dissolved in ethyl acetate (15 mL). The organic layer was washed with a saturated solution of NH$_4$Cl (1 × 5 mL) and brine (1 × 5 mL). The aqueous layer was successively stirred with ethyl acetate in order to recover any product dissolved in water. The organic phases were combined, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude mixture was used without purification for the next step.

General procedure for the preparation of oxazolidin-2-one (**26-27**)

A solution of 2-*N*-acetyl-1,3-propanediols **24a** or **25a** (0.2 mmol) in a mixture of toluene and diethylcarbonate (1:1, 2 ml) was refluxed for 1 h. After that, the solvent was evaporated under reduced pressure. To a stirred solution of this residue dissolved in a mixture of methanol and water (1:1, 3 mL), it was added LiOH (2 mmol). After 30 min, no starting material was detected by TLC analysis. Then, the solvent was evaporated under reduced pressure, and the residue dissolved in ethyl acetate (15 mL). The organic

phase was washed with distilled water (3 × 10 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. When R = 4-MeO-Ph-, no purification was needed because only one product was observed. However, when R = Ph-, a preparative plate was performed to separate the regioisomers. The eluent was a mixture (v:v:v) of hexane:methanol:dichloromethane (1:4.5:4.5).

Supplementary Information

Spectra of compounds synthesized in this manuscript are available free of charge at http://jbcs.sbq.org.br.

Acknowledgments

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