Tetrahedron: *Asymmetry* 24 (2013) 1063–1068

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric Diels–Alder cycloadditions of D-erythrose 1,3-butadienes to achiral *t*-butyl 2*H*-azirine 3-carboxylate

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A R T I C L E   I N F O

Article history:
Received 16 April 2013
Accepted 21 May 2013

A B S T R A C T

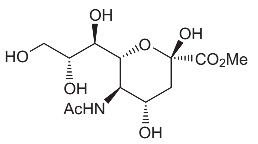
Two D-erythrose 1,3-butadienes were reacted with electrophilic achiral *t*-butyl 2*H*-azirine 3-carboxylate giving cycloadducts with good yields and moderate selectivity. The isomers could be separated to give the major (*R*)-isomers at C-2 in approximately 50% yield in both cases. Alternatively LACASA-DA methodology was applied to one of the reactions leading to homochiral (*R*)- and (*S*)-products by changing the chiral nature of an extra chiral BINOL inductor used.

1. Introduction

D-Erythrose is an important chiral synthon used in many syntheses.[1–5] However, the use of its 1,3-butadiene derivatives **1** is not common. The lack of interest in these dienes, namely as counterparts in Diels–Alder cycloadditions (DA), is probably due to the poor facial selectivity associated with DA thermal processes, although exceptions are known.[6,7] Nevertheless, a series of interesting compounds could be envisaged by functional group transformations (FGT) of these DA cycloadducts mainly in the field of sugars/aza-sugars. Therefore we attempted to better understand the facial selectivity of dienes **1** with dienophiles in order to improve the selectivity. At first, 5-membered ring dienophiles (maleimides and 4-phenyl/methyl-1,2,4-triazoline-3,5-dione) were examined. The major or exclusive isomer obtained [(*S*) at C-2] was formed by the attack of the dienophile at the *si* face of the diene.[7] Having in mind that the DA cycloadduct of D-erythrose-1,3-butadienes to 2*H*-azirines enables the synthesis of analogue precursors of neuraminic acid **3**, especially if the C-2 (*R*)-configuration isomers could be formed in reasonable yields, we tested this C=N dienophile to see if an approach by the *re* face would be preferred. Figure 1 represents the close relationship of neuraminic acid with the (*R*)-cycloadduct **4a**. Functionalization of the C=C bond would give an epimeric analogue of compound **3** at C-6.

2. Results and discussion

Two D-erythrose butadienes **1a**,**b** were prepared according to the literature[6,7] and combined with *t*-butyl 2*H*-azirine 3-carboxylate, obtained in situ from *t*-butyl α-azido acrylate;[9] the reaction occurs at 60 °C. Two products were formed in each reaction in the same ratio. Primary cycloadducts obtained by the reaction of diene **1b** lost the *t*-butyldimethylsilyl group attached to the erythrose moiety according to ^{1}H and ^{13}C NMR spectra, thus giving the free alcohols **4b** and **5b** (Scheme 1).



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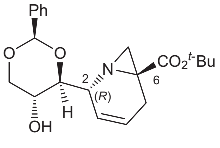

4a

Figure 1. Structural comparison of neuraminic acid **3** and (2*R*)-cycloadduct **4a**.

The regiochemistry of the cycloaddition results from the attack of the nucleophilic terminal of the diene to the electrophilic center in the azirine.[8] Such an approach can develop a hydrogen bond interaction between the nitrogen azirine ring atom of the dienophile and the hydroxyl group at the diene, favoring an attack at the *si* face (bottom representation in Fig. 2) over the *re* face (top

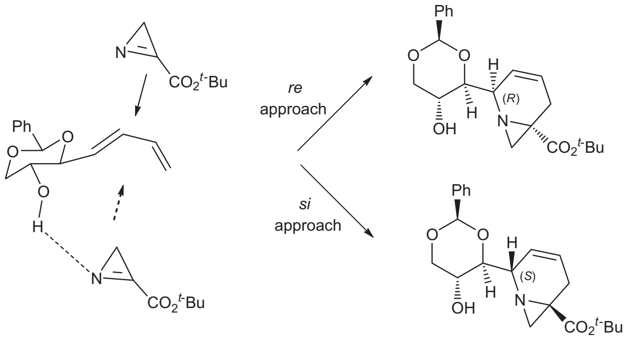

Figure 2. The *endo* facial approaches of 2*H*-azirine **2** to diene **1**.

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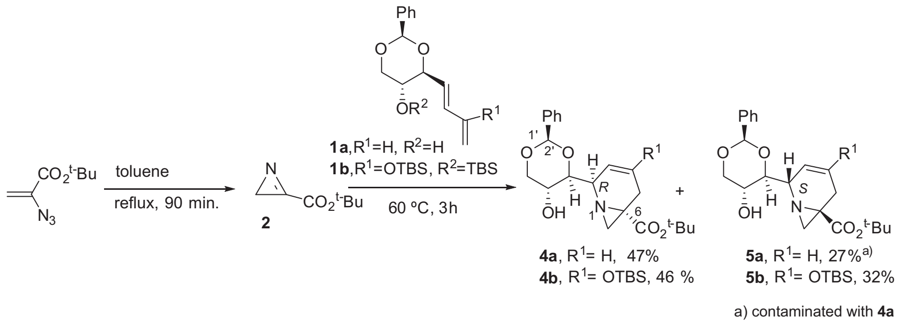
http://dx.doi.org/10.1016/j.tetasy.2013.05.015



Scheme 1. Thermal cycloaddition of 2*H*-azirine **2** to diene **1**.

representation depicted in Fig. 2). However the stereochemistry of the products is incompatible with such reagent interactions: an approximate (*R*):(*S*) ratio of 2.5:1 was obtained in the thermal reaction of diene **1a** to azirine **2** (Scheme 1).

The identification of the products (oils) was based on conformational analysis using molecular dynamics simulations. The two lowest free energy conformers of the (*R*)-diastereomer (structures **A** and **B**), and the (*S*)-diastereomer (structures **C** and **D**) were obtained. In every case, the hydroxyl group establishes an intramolecular hydrogen bond within *O*-1 in the dioxanyl moiety (Fig. 3). This obviously predicts the same *O*–H–*O* interaction trend to occur in the diene reagent, leaving no room for a possible hydrogen bond with the nitrogen atom of the approaching azirine that would favor the C-2 (*S*)-configuration product predicted by the approach outlined in Figure 2.

Figure 4 shows an alternative interaction of the approaching azirine to the *re*/*si* faces of the diene. The *re* approach shows a proximity between the nitrogen lone pair of the azirine and the π current of the aromatic ring. Attractive interactions at the van der Waals' distance were explored by using aromatic rings with a wide range of substituents in the triptycene scaffold.[10] Many examples of such a positive interaction have also been reported between the oxygen atom of carbonyls and the aromatic groups in proteins, within an average of 3.5 Å distance.[11] In the *si*-approach, the lone pair of the nitrogen is too far from the phenyl group due to the different directions of attack. The (*R*)-configuration product would also be favored from a kinetic profile point of view.

On the other hand, the conformational free energy difference between the (*R*)- and (*S*)-diastereomers using computational free energy perturbation methods was determined to be −8.9 kcal/mol, meaning that the (*S*)-product is thermodynamically preferred relative to the (*R*)-product. The isomeric ratio of products **4a**/**5a** probably reflects the major importance of kinetics over thermodynamics in this cycloaddition.

The identification of isomers **4a**/**5a** was made by measuring the dihedral angle between the two six-membered ring moieties in the more stable conformers **A**, **B** [(*R*)-isomer], and **C**, **D** [(*S*)-isomer]. (Fig. 3) Both **A** and **B** display small dihedral angles: **A** 68°, **B** 47°;

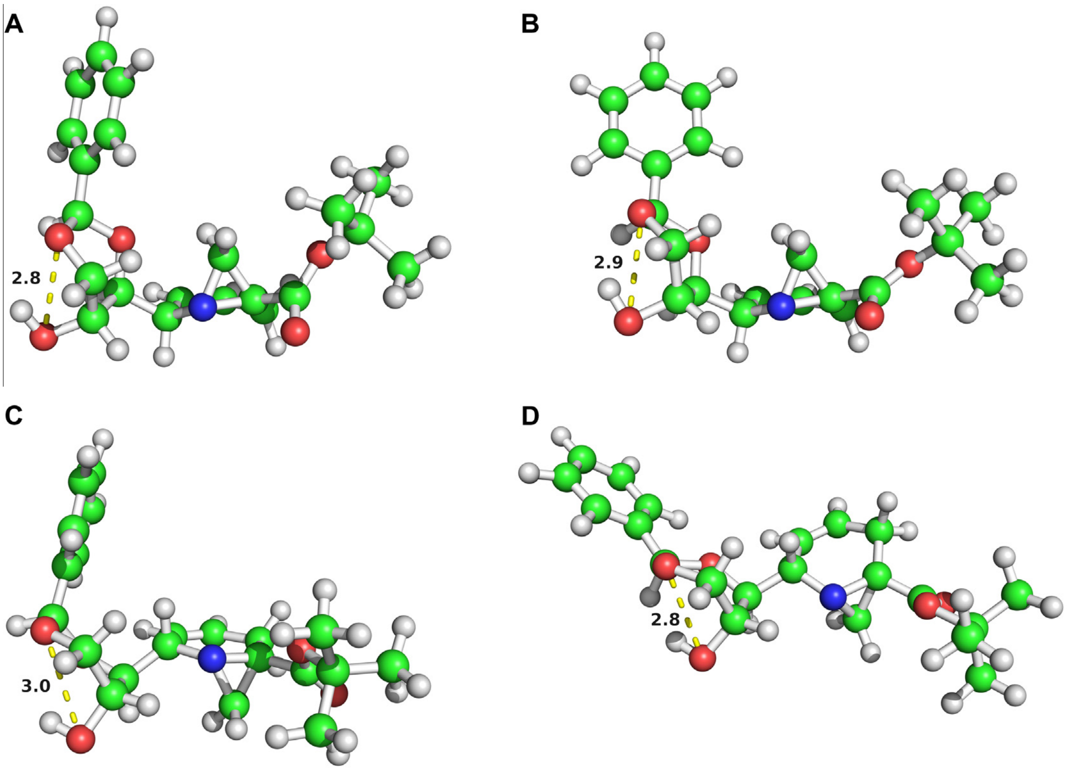


Figure 3. Lowest free energy conformations of (*R*)-**4a**/(*S*)-**5a**-diastereomers. (*R*)-Diastereomer: conformations **A** and **B**; (*S*)-diastereomer: conformations **C** and **D**. Structures are rendered in ball-and-stick mode with carbon in green, oxygen in red, nitrogen in blue, and hydrogen in white. Intra-molecular interactions and distances are highlighted with a dashed yellow line.

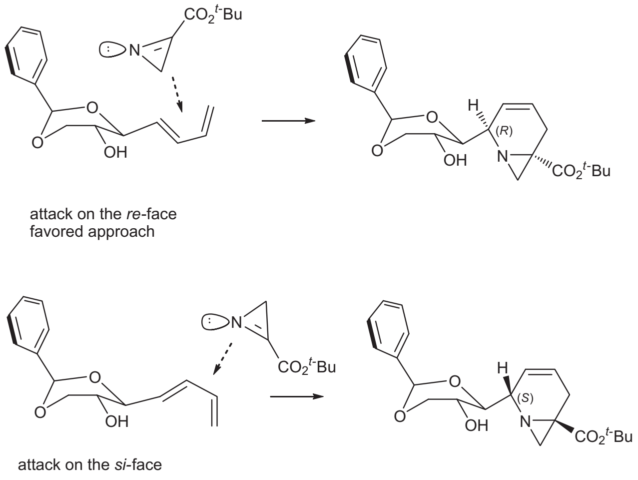


Figure 4. The two possible *endo* approaches of 2*H*-azirine **2** to diene **1a**.

these values are in accordance with the small coupling constant shown in the ^{1}H NMR spectrum (J ~2 Hz) for the (R)-diastereomer. Considering that conformers **A** and **B** make up 98% of the total population in chloroform an obvious relationship of the (R)-isomer with the small coupling constant of H-2 to H-4′ occurs. In contrast, **C** and **D** show larger dihedral angles: **C** 174°, **D** 176°, and so a large coupling constant of H-2 to H-4′ is predicted. In fact, the J is *ca* 10 Hz in the other (S)-isomer. The **C** and **D** population corresponds to 91% of the total conformation species solubilized in chloroform with 63% and 28%, respectively. An equivalent computational conformational analysis of compounds **4b**/**5b** was also made, however due to the lack of force field parameters for silicon, the *t*-butyldimethylsilyl group was replaced with *t*-butyl. The same dihedral angle/coupling constant trend was obtained for compounds **4b**/**5b**. The (R)-isomer shows 99% of its population to be in the **E** (89%) and **F** conformers (10%). The dihedral angles H–C$_2$–C$_4$–H in the two conformers are both small: 53° **E** and 61° **F**, which is consistent with the small coupling constant of H-2 to H-4′ (2.2 Hz) in the ^{1}H NMR spectrum. (Fig. 5) The (S)-isomer showed 94% of its population to be in the **G** conformer (74%) and **H** conformer (20%). The dihedral angles of these conformers are both large angles: 167° **G** and 162° **H**, which is consistent with the large coupling constant of H-2 to H-4′ (10.1 Hz). (Fig. 5).

With the aim of enhancing the formation of compound **4a** versus **5a**, we thought that a coordination reaction might induce kinetics to completely control the process. Previous experience with a bimetallic complex of Mg(II) and Zn(II) having (R)-/(S)-BINOL as a chiral ligand was applied in a Diels–Alder cycloaddition based on a Lewis acid-catalyzed reaction of a 'self-assembled' complex (LACASA-DA). This method involves with the existence of a free hydroxyl group in the diene and a carbonyl in the dienophile to coordinate all reagents and led to very good facial selectivities. 2,4-Pentadienol was combined with nitroso dienophiles,[12,13] and methyl acrylate[14,15] in the presence of tartaric acid or BINOL with excellent selectivities. We have previously reported on some control in reactions of diene **1a** with maleimides.[16]

Combining diene **1a** with azirine **2** at low temperatures gave homochiral compounds **4a** or **5a** depending on the stereochemistry of the BINOL (Scheme 2). Compound **5a** was obtained in 47% yield in the presence of (R)-BINOL, and **4a** in 28% yield in the presence of (S)-BINOL. The excess reacting diene remained untouched according to ^{1}H NMR spectra, even after the addition of fresh portions of azirine or prolonged reaction times.

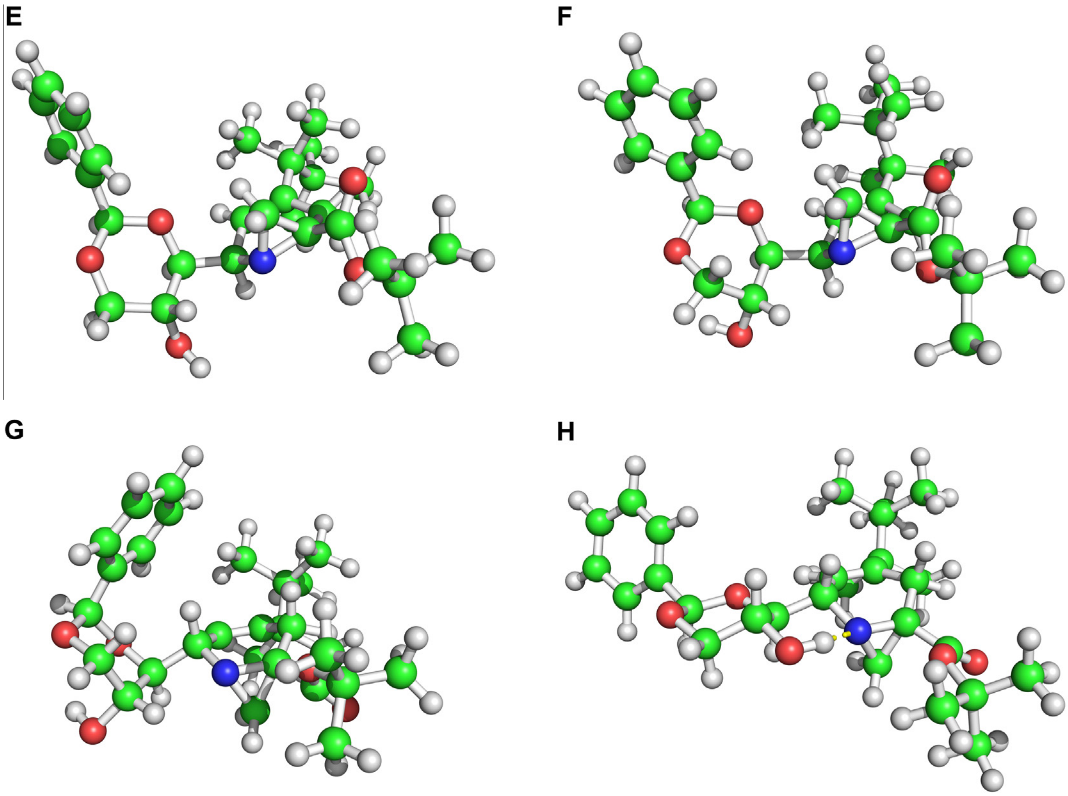
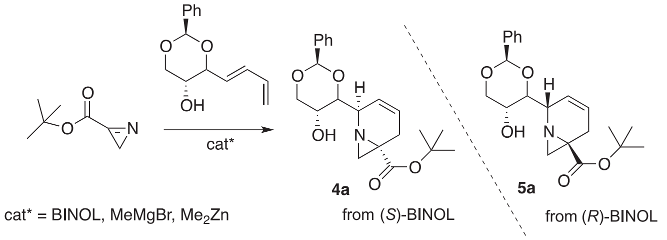


Figure 5. Lowest free energy conformations of the (R)-**4b**/(S)-**5b** diastereomers. (R)-Diastereomer: conformations **E** and **F**; (S)-diastereomer: conformations **G** and **H**. Structures as rendered in ball-and-stick mode with carbon in green, oxygen in red, nitrogen in blue, and hydrogen in white. Intra-molecular interactions and distances are highlighted with a dashed yellow line.



Scheme 2. The LACASA-Diels–Alder cycloaddition between diene **1a** and 2*H*-azirine **2** tethered in a bimetallic complex of Mg(II) and Zn(II) with (*R*)-/(*S*)-BINOL as a chiral ligand.

3. Conclusion

D-Erythrose 1,3-butadienes were combined with *t*-butyl 2*H*-azirine 3-carboxylate. Thermal reactions occur at 60 °C with moderate facial selectivity, favoring the (*R*)-enantiomer at C-2. The approach of the reagents has been inversed relative to other cases in the literature. The two (*R*)-products were separated to give the major isomer in 46% and 47% yield in cases **a** and **b** respectively. The moderate selectivity was explained by the antagonism of thermodynamics and kinetics of the cycloadditions. An LACASA-DA methodology using Zn/Mg bimetallic complexes and BINOL as an extra chiral inductor gave pure (*R*)- and (*S*)-products. A significant improvement in the yield was achieved in the case of the (*S*)-product but not in the (*R*)-product. The relative configuration of the new stereocenter in the products was obtained by combining the results of the conformational analysis with the ^{1}H NMR coupling constants.

4. Experimental

4.1. General

Starting with D-erythrose 1,3-butadienes **1a**,**b** were obtained from (2*R*,4*R*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxane-4-carbaldehyde according to the literature.[6,7] 2*H*-Azirine was prepared in situ from α-azido *t*-butyl acrylate.[9] All other reagents were purchased and used without further purification. Solvents employed in reactions were dried: CH_2Cl_2 was freshly distilled under CaH_2, and toluene was submitted to simple distillation to remove the head fraction. The petroleum ether 40–60 °C used in flash chromatography was previously distilled, while all other solvents were used as purchased. Glassware was dried prior to use. Compounds were purified by dry flash chromatography, using silica 60 <0.063 mm as the stationary phase and water pump vacuum. TLC plates (Silica Gel 60 F_{254}, Macherey–Nagel) were visualized either at a UV lamp or in I_2. ^{1}H NMR and ^{13}C NMR were run on a Varian Unity Plus 300, or Brucker Avance III 400 or Bruker BioSpin GmbH spectrometers. Infrared spectra were recorded on a Bomem MB 104 or on a Perkin–Elmer spectrophotometer. Samples were run as nujol mulls and oils as thin films. MS spectra were recorded on a VG Autospec M. spectrometer.

4.2. Reaction of L-erythrose diene 1a 1b to *t*-butyl 2*H*-azirine 3-carboxylate 2

4.2.1. Synthesis of cycloaducts 4a and 5a

4.2.1.1. Thermal method. The α-azido acrylate[9] (0.151 g; 0.893 mmol) was dissolved in toluene (16 mL) and refluxed under a nitrogen atmosphere for 90 min. The heating source was then removed and when the temperature reached 60 °C, a solution of diene **1a** (0.041 g; 0.177 mmol) in a 1:1 mixture of toluene/DCM (2 mL) was added. The mixture was maintained at 60 °C for 3 h. The solvent was evaporated until dryness and the crude subjected to flash chromatography in a 1:4 mixture of petroleum ether/ethyl ether. Two isomeric oily products were obtained. The (*S*)-isomer **5a**, (0.018 g; 0.048 mmol; 27%) was contaminated with the (*R*)-isomer **4a**, and (*R*)-**4a** was obtained pure (0.031 g; 0.083 mmol; 47%).

Isomer (*R*)-**4a**: $[\alpha]_D^{20} = -14.9$ (*c* 1.5, CH_2Cl_2); ν_{max} (neat) 3368, 2977, 1723, 1158 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42–7.45 (m, 2H, H*o*, Ph), 7.33–7.35 (m, 3H, H*m* and H*p*, Ph), 5.78 (ddt, *J* 10.4, 5.4, 3.4 Hz, 1H, H-4), 5.46–5.54 (m, 1H, H-3), 5.44 (s, 1H, H-2′), 4.38-4.50 (m, 1H, H-5′), 4.33 (dd, *J* 10.6, 5.3 Hz, 1H, H-6′), 4.20 (d, *J* 2.0 Hz, 1H, H-2), 3.77 (dd, *J* 9.3, 3.1 Hz, 1H, H-4′), 3.67 (t, *J* 10.4 Hz, 1H, H-6′), 2.65 (t, *J* 4.0 Hz, 2H, H-5), 2.36 (s, 1H, H-7), 2.06 (s, 1H, H-7), 1.48 (s, 9H, 3×CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 172.0 (C═O), 138.1 (Cq, Ph), 128.8 (C*p*, Ph), 128.1 (C*m*, Ph), 126.1 (C*o*, Ph), 123.6 (C-4), 123.5 (C-3), 101.4 (C-2′), 85.0 (C-4′), 81.6 (Cq, *t*-Bu), 81.5 (C-6), 71.1 (C-6′), 61.0 (C-5′), 53.0 (C-2), 36.8 (C-6), 30.9 (C-7), 28.0 (CH_3), 27.9 (CH_3), 27.8 (CH_3), 22.4 (C-5) ppm; HRMS (ESI): calculated for $C_{21}H_{28}NO_5$: 374.1960; found: 374.1962.

Isomer (*S*) **5a**: $[\alpha]_D^{20} = -11.2$ (*c* 1.05, $CHCl_3$); ν_{max} (neat) 3366, 2977, 1724, 1155 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47–7.50 (m, 2H, H*o*, Ph), 7.35–7.38 (m, 3H, H*m*+H*p*, Ph), 5.75–5.84 (m, 2H, H-3+H-4), 5.51 (s, 1H, H-2′), 4.38 (dd, *J* 10.8, 5.2 Hz, 1H, H-6′), 4.03 (ddd, *J* 10.1, 8.7, 5.2 Hz, 1H, H-5′), 3.96 (d, *J* 10.0 Hz, 1H, H-2), 3.69 (t, *J* 10.8 Hz, 1H, H-6′), 3.46 (dd, *J* 9.6, 8.4 Hz, 1H, H-4′), 2.67 (dd, *J* 4.4, 1.6 Hz, 2H, H-5), 2.22 (s, 1H, H-7), 2.00 (s, 1H, H-7), 1.47 (s, 9H, 3×CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 170.6 (C═O), 137.6 (Cq, Ph), 128.9 (C*p*, Ph), 128.2 (C*m*, Ph), 126.0 (C*o*, Ph), 123.8 (C-3 or C-4), 120.8 (C-3 or C-4), 101.0 (C-2′), 81.6 (Cq, *t*-Bu), 80.4 (C-4′), 70.5 (C-6′), 68.1 (C-5′), 59.9 (C-2), 39.4 (C-6), 27.9 (3×CH_3; C-7), 22.3 (C-5) ppm. HRMS (ESI): calculated for $C_{21}H_{28}NO_5$: 374.1952; found: 374.1962.

4.2.1.2. 2-LACASA-DA methodology

Solution A. A solution of diene **1a** (0.100 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (359 μL; 0.43 mmol) at 0 °C, and stirred for 5 min.

Solution B. A solution of (*S*)-BINOL (0.123 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of MeMgBr (1.4 M) in toluene/THF (307 μL; 0.43 mmol) at 0 °C, and stirred for 5 min.

Solution A was added to solution B, diluted with dry toluene (3.6 mL), and stirred for 5 min. This mixture was cooled to −78 °C and a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.061 g; 0.43 mmol) in dry toluene (3 mL) was then added. The reaction was stirred at −20 °C for 24 h. A new portion of *t*-butyl 2*H*-azirine-3-carboxylate was then added and the reaction was stirred at rt for 5 days. The reaction was quenched with $NaHCO_3$ aq satd sol. (1 mL), filtered through a pad of Celite®, and the Celite® was washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give an orange oil corresponding to a 2:1 mixture of diene starting material and the expected product. The crude was submitted to 'dry-flash' chromatography using a mixture of PE (40–60)-Et_2O. The (*S*)-BINOL was recovered from PE–Et_2O 1:1 (0.069 g; 56%) and the product was eluted with PE/Et_2O 2:3 to give the (*R*)-isomer as an oil (0.044 g; 28%).

4.2.2. Synthesis of cycloadducts 4b and 5b

4.2.2.1. Thermal method. The *t*-butyl α-azido acrylate (0.340 g; 2.01 mmol) was dissolved in toluene (30 mL) and refluxed under a nitrogen atmosphere for 90 min. The heating source was removed and when the reaction mixture temperature reached 60 °C, a solution of diene **1b** (0.184 g; 0.386 mmol) in DCM (4 mL) was added. The mixture was maintained at 60 °C for 5 h. A second portion of azirine was prepared (0.180 g; 1.06 mmol) in dry toluene (18 mL) and added to the reaction mixture and stirred further at 60 °C for 1.5 h. The solvent was evaporated until dryness, after which flash chromatography was carried out using petroleum ether/ethyl ether 30% as the eluent. Two isomeric compounds were obtained in 78% overall yield, and separated as oils: (*S*)-isomer **5b** (0.063 g; 0.125 mmol; 32%) and (*R*)-isomer **4b** (0.090 g; 0.179 mmol; 46%).

Isomer (*R*)-**4b**-viscous oil. $[\alpha]_D^{20} = -40.5$ (*c* 1.05, $CHCl_3$); ν_{max} 3746, 3682, 3093, 3067, 3037, 3005, 1727, 1678, 1164, 1135, 1090, 1030, 841 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 7.47–7.42 (m, 2H, CH, Ph), 7.38–7.31 (m, 3H, CH, Ph), 5.43 (s, 1H, H-2′), 4.58 (br t, *J* 2.2 Hz, 1H, H-3), 4.41 (td, *J* 9.8, 5.4 Hz, 1H, H-5′), 4.33–4.37 (m, 2H, H-6′+H-2), 3.70–3.66 (m, 2H, H-4′+H-6′), 2.74 (d, *J* 17.7 Hz, 1H, H-5), 2.64 (br s, 1H, O*H*), 2.54 (d, *J* 17.8 Hz, 1H, H-5), 2.30 (s, 1H, H-7), 2.06 (s, 1H, H-7), 1.50 (s, 9H, $OCCH_3$), 0.92 (s, 9H, $SiCCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C=O), 147.3 (C-4), 138.1 (Cq, Ph), 128.7 (CH, Ph), 128.1 (CH, Ph), 126.0 (CH, Ph), 101.3 (C-2′), 99.2 (C-3), 84.9 (C-4′), 81.7 (Cq), 71.1 (C-6′), 61.3 (C-5′), 54.0 (C-2), 38.4 (Cq, *t*-Bu), 30.9 (C-7), 28.0 (C-*C*H3), 27.7 (C-5), 25.6 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), −4.4 ($SiCH_3$), −4.6 ($SiCH_3$) ppm; HRMS (FAB): calculated for $C_{27}H_{42}NO_6Si$: 504.2781; found: 504.2786.

Isomer (*S*)-**5b**: viscous oil. $[\alpha]_D^{20} = -4.0$ (*c* 1.8, $CHCl_3$); ν_{max} (neat) 3566, 3554, 3092, 3068, 3036, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H, C-H, Ph), 7.40–7.33 (m, 3H, C-H, Ph), 5.52 (s, 1H, H-2′), 4.91–4.84 (m, 1H, H-3), 4.38 (dd, *J* 10.8, 5.2 Hz, 1H, H-6′), 4.07 (d, *J* 9.7 Hz, 1H, H-5′), 4.00 (ddd, *J* 10.1, 8.7, 5.2 Hz, 1H, H-2), 3.68 (t, *J* 10.8, 1H, H-6′), 3.42 (dd, *J* 9.5, 8.8 Hz, 1H, H-4′), 2.77 (dtd, *J* 17.6, 2.5, 1.1 Hz, 1H, H-5), 2.56 (dd, *J* 17.6, 0.7 Hz, 1H, H-5), 2.21 (s, 1H, H-7), 1.99 (s, 1H, H-7), 1.47 (s, 9H, $OC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.16 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C=O), 148.1 (C-4), 137.6 (Cq, Ph), 128.8 (CH, Ph), 128.2 (CH, Ph), 125.8 (CH, Ph), 100.7 (C-2′), 95.8 (C-3), 81.8 (Cq), 81.2 (C-4′), 70.4 (C-6′), 68.0 (C-2), 60.4 (C-5′), 40.9 (Cq, *t*-Bu), 28.2 (C-7), 28.1 (C-5), 27.9 (C-CH_3), 25.6 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), −4.4 ($SiCH_3$), −4.5 ($SiCH_3$) ppm; HRMS (FAB): calculated for $C_{27}H_{42}NO_6Si$: 504.2781; found: 504.2779.

4.2.2.2. LACASA-DA methodology

Solution A. A solution of diene **1a** (0.100 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of Me_2Zn (1.2 M) in toluene (359 μL; 0.43 mmol) at 0 °C, and stirred for 5 min.

Solution B. A solution of (*R*)-BINOL (0.123 g; 0.43 mmol) in dry toluene (2.2 mL) was added to a solution of MeMgBr (1.4 M) in toluene/THF (307 μL; 0.43 mmol) at 0 °C, and stirred for 5 min.

Solution A was added to solution B, diluted with dry toluene (3.6 mL), and stirred for 5 min. This mixture was cooled to −78 °C and a solution of *t*-butyl 2*H*-azirine-3-carboxylate (0.061 g; 0.43 mmol) in dry toluene (3 mL) was added. After mixing the reagents, the temperature was allowed to rise gradually to rt. The reaction was quenched with $NaHCO_3$ aq. satd. sol. (1 mL), filtered through a pad of Celite®, and the Celite® washed with EtOAc (4 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give an orange oil, consisting of a 1:1 mixture of starting diene and product. The crude was submitted to 'dry-flash' chromatography using a mixture of PE (40–60)–Et_2O. The (*R*)-BINOL was recovered from PE–Et_2O 3:1 (0.076 g; 62%) and the product was eluted with PE–Et_2O 1:1 to give the (*S*)-isomer as an oil (0.076 g; 47%).

5. Materials and methods

Molecular dynamic (MD) simulations were performed with the GROMACS package version 4.5.4 using an AMBER03/GAFF force field. The geometry of each azirine enantiomer was optimized with a quantum mechanical method at the Hartree–Fock level with the 6-31G(d) basis set using GAMESS. This optimized geometry and the quantum mechanical electrostatic potential were used to calculate the partial atomic charges using the RESP fitting method. The azirine molecules were solvated with 500 chloroform solvent molecules in a cubic box with dimension of 4.4 × 4.4 × 4.4 nm. The equations of motion were numerically integrated using a time-step of 2 fs. The nonbonded interactions were treated with a cut off of 0.9 nm and updated every 5 steps. Long-range electrostatic interactions were treated with particle-mesh-ewald (PME) using a fourier spacing of 1.2 nm and a PME order of 4. The system was simulated in an isothermal and isochoric ensemble using the Berendsen thermostat at 300 K and relaxation time of 0.1 ps. The pressure coupling was also accomplished with the Berendsen barostat with a relaxation time of 0.5 ps and isothermal compressibility of 4.5×10^{-5} bar. All bonds were constrained using the LINCS algorithm. An initial energy minimization consisting of 5000 steps was performed using the steepest descent algorithm. We performed one long MD simulation of 400 ns for each system. Conformations were recorded every 1 ps.

From these long MD simulations the multidimensional free energy landscape of each azirine enantiomer was calculated. The multidimensional free energy landscape was calculated using a principal component analysis (PCA) approach based on the structural dissimilarity of all pairs of conformations recorded. The protocol for the PCA calculations and identification of the lowest free energy conformations used herein was the same as described by Sara et al.[17]

Acknowledgments

We thank FCT for project funding PTDC/QUI/67407/2006, for financial support to the NMR portuguese network (PTNMR, Bruker Avance III 400-Univ. Minho); FCT and FEDER (European Fund for Regional Development)-COMPETE-QREN-EU for financial support to the Research Centre, CQ/UM [PEst-C/QUI/UI0686/2011 (FCOMP-01-0124-FEDER-022716)]. N.M. acknowledges the contract research program 'Compromisso com a Ciência' reference: C2008-UMINHO-CQ-03 and access to the Minho University GRIUM cluster. V.C.M.D. also thanks for PhD grant (SFRH/BD/61290/2009).

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