Available online at www.sciencedirect.com
ScienceDirect
Journal of Organometallic Chemistry 693 (2008) 1136–1142
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis of unnatural cyclitols via a combined enzymatic-palladium catalysis approach

Ana Bellomo [a], David Gonzalez [a,*], Hèlio A. Stefani [b,*]

[a] Departamento de Química Orgánica, Facultad de Química, UdelaR, General Flores 2124, C.C. 1157 Montevideo, Uruguay
[b] Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP, Brazil

Received 12 October 2007; received in revised form 5 January 2008; accepted 5 January 2008
Available online 11 January 2008

Abstract

The Suzuki–Miyaura cross-coupling reaction of a hydroxylated vinyl bromide obtained by a chemoenzymatic approach with a diverse range of potassium organotrifluoroborates has been accomplished catalyzed by $Pd(PPh_3)_4$ in satisfactory yields. A variety of functional groups are tolerated in the nucleophilic partner.

Keywords: Suzuki–Miyaura cross-coupling reaction; Potassium organotrifluoroborate salts; Conduritol nucleus; Biocatalysis

1. Introduction

Although the development of organic chemistry in the past century has been immense, there are still limitations in the effectiveness of the traditional synthetic approach to the manufacture of valuable molecules and natural products. In addition, environmental concerns about the traditional organic methodology has become a major drawback for the further development of synthetic chemistry. Biotechnology, overcomes some of these issues but, at the present state of knowledge, it cannot completely substitute traditional organic methods. As a consequence, the combination of the two methodologies in a single strategy results in one of the most effective approaches for the efficient preparation of relevant natural products and high added-value molecules.

There is a growing interest in the generation of diversity by means of simple albeit efficient reactions. Enantiopure compounds of medium complexity, that resemble natural products are on demand as potential leads for the pharmaceutical and agrochemical industries. Therefore, we have embraced the search for a short strategy to generate families of compounds containing several chiral centers and tunable lipophilicity by the combination of the Suzuki–Miyaura coupling and biotransformations demonstrating the complementary nature of biocatalysis and organometallic chemistry.

Boronic acids and boronate esters are the most commonly used nucleophiles in Suzuki cross-coupling reactions. However, several groups have explored the use of potassium organotrifluoroborate salts (RBF_3K) as an alternative to these boron reagents in Suzuki coupling reactions [1]. These salts are readily prepared by the addition of an aqueous solution of inexpensive, widely available KHF_2 to an ample variety of organoboron intermediates [2].

We made use of the power of enzymatic catalysis to incorporate chirality into an aromatic ring and prepared a conduritol nucleus by the well known toluene dioxygenase oxidation of arenes [3] followed by chemical oxidation and azidolysis.

The library of compounds to be synthesized will contain an azide functionality which could be used to generate triazoles by the well-known Huisgen procedure and it could

* Corresponding authors. Tel.: +5982 929 01 06 (D. Gonzalez); fax: +55 11 30913654 (H.A. Stefani).
E-mail addresses: davidg@fq.edu.uy (D. Gonzalez), hstefani@usp.br (H.A. Stefani).

0022-328X/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2008.01.006

also be reduced to an amino group so as to incorporate amino acidic units in the conduritol moiety by amidation reactions.

2. Results and discussion

We first exposed bromobenzene (**1**) to a culture of the mutant strain *Pseudomonas putida* 39/D in order to generate a *cis*-cyclohexadiene diol with very high regio- and enantioselectivity. The resulting bromodiene diol (**2**) has been extensively exploited by Hudlicky [4], Banwell [5], and others [6] to synthesize a varied array of natural and unnatural compounds in step-economic sequences.

We have previously used this reaction for the preparation of inositols [7], aminoconduritols [8] and sulfur containing cyclitol analogs [9] introducing the required functionality in the cyclohexadiene nucleus in a stereospecific fashion by standard chemical means. One of the best procedures to do this is the epoxidation of a protected derivative to furnish oxirane (**3**) with complete regio- and stereospecifity [10]. Furthermore, alternative strategies to achieve these functionalizations involve a palladium-catalyzed *trans*-diacetoxylation of a protected 3,5-cyclohexadiene-1,2-diol [11]. The resulting epoxide **3** is subjected to an azidolysis reaction rendering hydroxyazide (**4**) which was envisioned to be a very useful intermediate because it can be further functionalized [12] and the vinyl bromide moiety can operate as partner in a palladium-catalyzed Suzuki cross-coupling reaction.

The efficiency and advantages of the organotrifluoroborates in a variety of cross-coupling reactions have been already established [13] so we sought to extend their utility to systems not previously studied. Herein, we report the palladium-catalyzed Suzuki cross-coupling reactions carried out between the required RBF_3K and vinyl bromide (**4**) to produce trisubstituted olefines of type **5** (Scheme 1).

Molander and co-workers have described several procedures for the coupling of RBF_3K with a range of electrophiles and have shown the vast scope of these reagents and simplified the coupling protocols [14]. However, there are only few reports in the literature referring to the use of *cis*-cyclohexadiene diols in Suzuki couplings [6b,15] and to the best of our knowledge, this article describes the first example where these diols are used as electrophilic partners to be coupled with aryltrifluoroborates.

Our initial studies of this process focused on developing the best set of reaction conditions for the palladium catalyzed cross-coupling of RBF_3K with vinyl bromide (**4**). For this purpose we used an electron-neutral organotrifluoroborate (phenyltrifluoroborate) as the test case.

The results showed that the choice of the catalyst and solvent was crucial. Palladium (II) and (0) species were employed in the cross-coupling reaction and the best results were reached with the Pd(0) catalyst (Table 1). The use of $PdCl_2(dppf)CH_2Cl_2$ in THF or DMF as well as the ligand system $Pd(OAc)_2$/DPE phos in MeOH did not render the desired product (Table 1, entries 1, 2 and 4). However, $PdCl_2(dppf)CH_2Cl_2$ in THF–H_2O and $Pd(OAc)_2$/2-(di-*t*-butylphosphino)biphenyl in MeOH did show product formation although in modest yields (Table 1, entries 3 and 5). The more reactive $Pd(PPh_3)_4$ in toluene–H_2O proved to be the superior choice so it was selected as the palladium source for the following experiments (Table 1, entries 6–9).

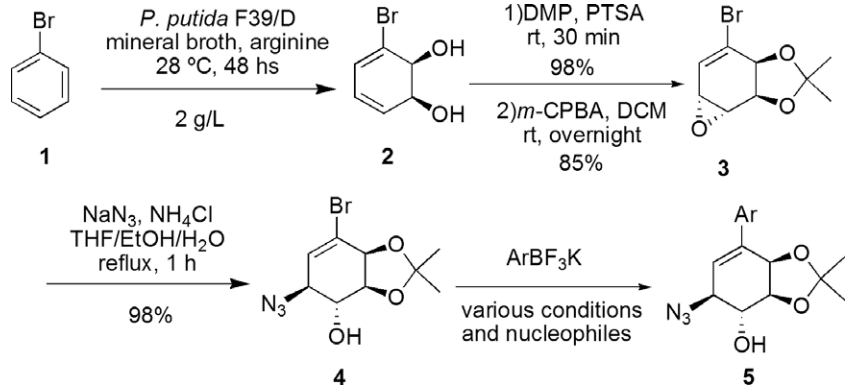
Table 1
Catalyst and solvent optimization of the cross-coupling reaction of potassium phenyltrifluoroborate with hydroxyazide (**4**)

Entry	Pd source (mol%)	Ligand (mol%)	Solvent	Yield (%)
1	$PdCl_2(dppf)CH_2Cl_2$ (10)	None	THF	
2	$PdCl_2(dppf)CH_2Cl_2$ (10)	None	DMF	
3	$PdCl_2(dppf)CH_2Cl_2$ (10)	None	THF–H_2O	45
4	$Pd(OAc)_2$ (3)	DPE phos (6.5)	MeOH	
5	$Pd(OAc)_2$ (3)	2-(di-*t*-butilfosfino)-bifenilo (6.5)	MeOH	35
6	$Pd(PPh_3)_4$ (2)	None	Toluene–H_2O	70[a]
7	$Pd(PPh_3)_4$ (4)	None	Toluene–H_2O	70[b]
8	$Pd(PPh_3)_4$ (6)	None	Toluene–H_2O	64
9	$Pd(PPh_3)_4$ (10)	None	Toluene–H_2O	65

Reaction conditions: vinyl bromide (**4**) (1 mmol), $PhBF_3K$ (1.2 equiv.), Cs_2CO_3 (3 equiv.). Entries 1–3: reflux; entries 4–5: rt to reflux; entries 6–9: 90 °C.

[a] Product **5a**/starting material **4**: 1/1 (NMR conversion).

[b] Product **5a**/starting material **4**: 7/3 (NMR conversion).



Scheme 1. Chemoenzymatic preparation of the azidoconduritol derivative **4** and olefines **5**.

Among the tested solvents, toluene–H_2O was far the most effective system. The critical role of water has been previously noted [16]. In fact, water facilitates the solubilization of the components of the coupling reaction. It is a well documented fact that solubilization is accomplished at the expense of promoting the protiodeborination of the potassium salt [17], thus a delicate balance must be reached. We found that the reaction of potassium phenyltrifluoroborate with **4** and $Pd(PPh_3)_4$ in a 1/3.5 water/toluene mixture provided the cross-coupled product in very good yield.

The use of $Pd(PPh_3)_4$ in 3.5/1 toluene–H_2O mixture was employed to study the effect of catalyst loading (Table 1, entries 6–9). The best result was achieved when 6 mol% of catalyst was used (Table 1, entry 8). Simply rising the mol percentage of catalyst from 2% to 6% resulted in the complete conversion of **4**–**5a** in 64% yield along with only 10% of the homocoupling side product. When 4 mol% of catalyst was employed, results comparable to 2 mol% were obtained. With catalyst loading above the optimum (Table 1, entry 9) the starting material was still used up, but the percentage of homocoupled product was found to be 15%. This illustrates the best amount of catalyst needed for the reaction to be efficient.

Next, we turned our attention to the study of the influence of other parameters such as nature of the base and reaction temperature. The cross-coupling reactions in all studied reaction cases were performed in the presence of 3 equiv. of base [18]. Several inorganic bases were surveyed. Na_2CO_3 did not render the desired product at any temperature (Table 2, entries 1 and 2) and K_2CO_3 showed little cross-coupling product formation (Table 2, entry 3). Cs_2CO_3 afforded the best result working at 90 °C while lower reaction temperatures were ineffective or inefficient.

Careful analysis of the reaction data revealed that the best conditions for the coupling were the use of vinyl bromide **4** (1 mmol), RBF_3K (1.2 equiv.), $Pd(PPh_3)_4$ (6 mol%) and Cs_2CO_3 (3.0 equiv.) diluted in toluene/H_2O (3.5/1), under heating at 90 °C.

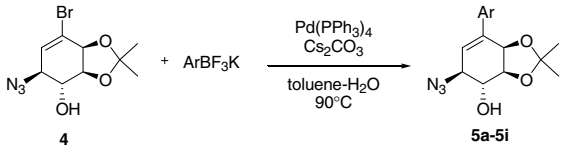
To probe the scope of these optimized conditions we extended the coupling reaction to other representative potassium organotrifluoroborates and the results obtained are summarized in Table 3.

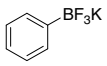
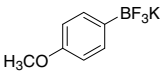
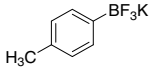
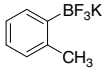
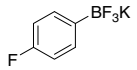
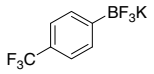
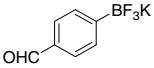
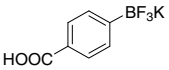
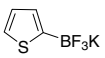
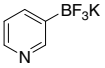
Table 2
Activator and temperature optimization in the cross-coupling reaction of potassium phenyltrifluoroborate with hydroxyazide (**4**)

Entry	Base	*T* (°C)	Yield (%)
1	aq. Na_2CO_3	50	
2	aq. Na_2CO_3	70	
3	K_2CO_3	50	35
4	K_2CO_3	Reflux	Decomposition
5	Cs_2CO_3	rt	Recovered s.m.
6	Cs_2CO_3	50	45
7	Cs_2CO_3	90	64

Reaction conditions: vinyl bromide (**4**) (1 mmol), $PhBF_3K$ (1.2 equiv.), $Pd(PPh_3)_4$ (6 mol%), toluene/H_2O (3.5/1).

Table 3
Coupling of functionalized potassium trifluoroborates with hydroxyazide (**4**)



Entry	$ArBF_3K$	Time (h)	Isolated yield **5**: (%) (homocoupling)
1		2.0	**5a**: 64 (10)
2		2.0	**5b**: 71 (8)
3		1.7	**5c**: 70 (7)
4		8.0	**5d**: 60 (20) prod./s.m.: 3/2
5		4.5	**5e**: 62 (30)
6		6.5	**5f**: 57 (23)
7		3.0	**5g**: 45 (21)
8		9.0	Recovered s.m.: 40 (20)
9		5.5	**5h**: 50 (14)
10		10.0	**5i**: 43 (20)[a] prod./s.m.: 2/1
11		24.0	Recovered s.m.: 85

Reaction conditions: vinyl bromide (**4**) (1 mmol), RBF_3K (1.2 equiv.), $Pd(PPh_3)_4$ (6 mol%) (unless otherwise noted), Cs_2CO_3 (3 equiv.), toluene/H_2O (3.5/1), 90 °C.

[a] Results obtained using 10 mol% of the catalyst.

The reaction proceeded with satisfactory yields in most cases and it was tolerant to a variety of functional groups. Compatibility was demonstrated with fluoro, ether and aldehyde groups. Coupling reactions with electron-rich potassium aryltrifluoroborates proceeded in very good yields. Potassium 4-methylphenyltrifluoroborate was the best substrate, with the product **5c** obtained in 70% isolated yield in less than 2 h (Table 3, entry 3).

Even electron-withdrawing substituted aryltrifluoroborate salts afforded the corresponding products (Table 3, entries 5–7). As outlined in entry 7, the presence of an aldehyde group did not preclude the cross-coupling reaction. However, the yield of product was lower than 50% in this case (Table 3, entry 9). Less reactive RBF_3K (Table 3, entry 8) led to recovery of the vinyl bromide starting material and the sterically encumbered *ortho*-methylsubstituted substrate (Table 3, entry 4) reacted slowly, with only partial conversion to **5d**. This compound exhibited very similar chromatographic behaviour with the starting vinyl bromide **4** and therefore could not be isolated in its pure state. This result showed that the reaction is very sensitive to hindered substrates as it is documented for some Suzuki–Miyaura cross-couplings [19]. Potassium 4-methoxyphenyltrifluoroborate and potassium 4-fluorophenyltrifluoroborate were tested as substrates that bear substituents with π-releasing but inductively electron-withdrawing characteristics. The results obtained in these cases indicated that the reactions provided the desired products **5b** and **5e** in good yields and just after a few hours of reaction (Table 3, entries 2 and 5).

Continuing with our investigation, we explored the reaction of bromide **4** with heteroaryltrifluoroborates. Although potassium 3-thiophenetrifluoroborate could be used with success, the cross-coupling of a 3-pyridyl nucleophile rendered only recovered starting material (Table 3, entry 11) and all the attempts to couple potassium 2-thiophenetrifluoroborate with **4** rendered the desired product along with the starting vinyl bromide which could not be separated from the product (Table 3, entry 10). Increasing the catalyst loading from 6 to 10 mol% had no effect in reaching total conversion suggesting that for this demanding substrate more forcing conditions are required.

3. Conclusion and outlook

In summary, palladium-catalyzed cross-coupling reactions of a range of potassium organotrifluoroborates with vinyl bromide (**4**) have been efficiently achieved, using low catalyst loadings. More importantly, the coupling turned out to be general with respect to a diverse array of functionality although in the case of very unreactive compounds we were not able to establish the best conditions that would led to total conversion of the starting materials in the desired products. We are currently working in improving the yield of this reaction and in the further functionalization of the conduritol moiety to attain a diversity oriented collection of cyclitol conjugates.

4. Experimental

All solvents were purified prior to use. Melting points were determined on a Büchi B-545 apparatus and are uncorrected. Optical rotations were measured at 589 nm on a Perkin–Elmer 343 automatic polarimeter using a 1 mL cell (concentration *c* given in g/100 mL). Infrared spectra (IR) were recorded on a Varian 1000 FT-IR spectrometer and peaks are reported in reciprocal cm along with relative signal intensities and characteristics: s (strong); m (medium); w (with). Low-resolution mass spectra were performed on a Bruker Daltonics model Esquire HCT (ESI-MS, ion trap) and on a Shimadzu GCMS-QP5050A and molecular ion peaks are listed with relative abundances. High-resolution mass spectra were performed on a Bruker Daltonics model TOF_{LC} (ESI + mode). Nuclear magnetic resonance spectra were recorded on Bruker Avance DPX-300 instrument with tetramethylsilane as internal standard and chloroform-*d* as solvent. Chemical shifts (δ) are recorded in ppm and coupling constants (J) are reported in Hertz. Retention factors (R_f) are reported for analytical thin layer chromatography performed on aluminium plates treated with F-254 indicator. Visualization was accomplished with the aid of UV light and/or vanillin–H_2SO_4–MeOH as the detecting agent. Flash column chromatography were carried out using silica gel (Kieselgel 60, EM Reagents, 230–400 mesh).

Potassium organotrifluoroborate salts (4-fluorophenyl, 4-(trifluoromethyl)phenyl, 4-formylphenyl, 4-carboxyphenyl, and 3-thiophene) were obtained from commercial sources while other derivatives (phenyl, 4-methylphenyl, 2-methylphenyl, 4-methoxyphenyl, 2-thiophene, and 3-pyridine) were prepared according to the literature procedures [20]. $Pd(PPh_3)_4$ was prepared following the procedure described in the literature [21].

4.1. General procedure for Suzuki–Miyaura cross-coupling reactions of vinyl bromide (4) and potassium organotrifluoroborates

Cs_2CO_3 (0.750 mmol, 3.0 equiv.), $Pd(PPh_3)_4$ (0.015 mmol, 6%), potassium organotrifluoroborate (0.275 mmol, 1.1 equiv.) and vinyl bromide (**4**) (0.25 mmol, 1.0 equiv.) were added to a flame-dried two-necked flask equipped with a condenser. The system was purged with N_2 for 2 min. The solvents (0.75 mL of toluene and 0.2 mL of H_2O) were added and the mixture was put in an oil bath previously set at 90 °C.

The reaction mixture was stirred for the appropriate time indicated in Table 3. Once the reaction was completed, it was diluted with hexanes and $MgSO_4$ was added. The organic layer was removed and the remaining $MgSO_4$ paste was triturated two times with hexanes and thrice with ethyl acetate. The combined organic extracts were placed directly into a plug of silica gel to remove the catalyst, thus yielding the crude product. Further purification was accomplished via column chromatography using a gradient of hexanes/ethyl acetate (85/15, 80/20, and 70/30).

4.1.1. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(phenyl)cyclohex-3-ene-1-ol (**5a**)

White crystalline solid. M.p.: 123–124 °C. $[\alpha]_D^{24}$ + 9.78 (*c* 0.755, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.55 (d, J_{o-m} = 7.02, 2 H, H*o*), 7.34 (m, 3H, H*m* and H*p*), 6.07 (d, J_{3-2} = 1.29, 1H, H3), 5.04 (d, J_{5-6} = 5.97, 1H, H5), 4.20 (dd, J_{6-5} = 6.18, J_{6-1} = 9.06, 1H, H6), 4.07 (bd, J_{2-1} = 9.06, 1H, H2), 3.80 (t, J_{1-2} = 9.03, J_{1-6} = 9.12, 1H, H1), 2.91 (bs, 1H, OH), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 136.97 (C4), 135.82 (C arom.–C4), 128.67 (di, C (H*m*)), 128.57 (C (H*p*)), 126.15 (di, C (H*o*)), 125.38 (C (H3)), 110.75 (C isopropylidene), 78.18 (C (H6)), 73.42 (C (H5)), 73.37 (C (H1)), 62.27 (C (H2)), 28.46 (CH_3), 26.07 (CH_3). IR (neat): 3441 (O–H, w), 2091 (N_3, s), 1255 (s), 1208 (C–N, m), 1061 (C–O–C, s), 875 (C–H, s), 810 (C=C, s). GC–MS: 201 ($M^+-C_3H_6O-N_2$, 22), 172 (43), 130 (M^+−Ph–2H_2O–N_3, 100), 77 (Ph, 19), 58 (C_3H_6O, 10). TLC: R_f 0.48 (hexane/EtOAc, 70/30). HRMS: *m*/*z* calc. for $(C_{15}H_{17}N_3O_3Na)^+$: 310.1162. Found: 310.1160%.

4.1.2. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(4-(methoxy)phenyl)cyclohex-3-ene-1-ol (**5b**)

White crystalline solid. M.p.: 147–149 °C. $[\alpha]_D^{24}$ + 11.96 (*c* 0.605, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.50 (d, J_{m-o} = 8.28, 2H, Hm_{OCH_3}), 6.90 (d, J_{o-m} = 8.31, 2H, Ho_{OCH_3}), 5.98 (bs, 1H, H3), 5.02 (d, J_{5-6} = 5.52, 1H, H5), 4.19 (t, J_{6-5} = 6.69, J_{6-1} = 8.19, 1H, H6), 4.07 (bd, J_{2-1} = 8.82, 1H, H2), 3.82 (bs, 4 H, H1 and CH_3 (OCH_3 arom.)), 3.05 (bs, 1H, OH), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 159.88 (C arom.–OCH_3), 135.08 (C4), 129.45 (C arom.–C4), 127.40 (di, C (Hm_{OCH_3})), 123.35 (C (H3)), 114.04 (di, C (Ho_{OCH_3})), 110.92 (C isopropylidene), 78.21 (C (H6)), 73.44 (di, C (H1) and C (H5)), 62.25 (C (H2)), 55.32 (C (OCH_3)), 28.10 (CH_3), 26.07 (CH_3). IR (neat): 3460 (O–H, w), 2091 (N_3, s), 1250 (s), 1193 (C–N, m), 1058 (C–O–C, s), 875 (C–H, s), 817 (C=C, s). GC–MS: 216 ($M^+-C_3H_6O-N_3$, 8), 109 ($M^+-C_3H_6O-N_3-OCH_3Ph$, 6), 96 (Ph+H_2O, 10), 77 (Ph, 9), 58 (C_3H_6O, 20), 43 ($N_2 + CH_3$, 100). TLC: R_f 0.46 (hexane/EtOAc, 70/30). HRMS: *m*/*z* calc. for $(C_{16}H_{19}N_3O_4Na)^+$: 340.1268. Found: 340.1266%.

4.1.3. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(4-(methyl)phenyl)cyclohex-3-ene-1-ol (**5c**)

White crystalline solid. M.p.: 1119–121 °C. $[\alpha]_D^{24}$ + 9.66 (*c* 0.595, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.43 (d, J_{m-o} = 8.13, 2H, Hm_{CH_3}), 7.16 (d, J_{o-m} = 8.01, 2H, Ho_{CH_3}), 6.01 (d, J_{3-2} = 1.80, 1H, H3), 5.02 (d, J_{5-6} = 5.94, 1H, H5), 4.17 (dd, J_{6-5} = 6.09, J_{6-1} = 9.12, 1H, H6), 4.05 (d, J_{2-1} = 9.03, 1H, H2), 3.77 (t, J_{1-2} = 9.09, J_{1-6} = 9.09, 1H, H1), 2.79 (bs, 1H, OH), 2.34 (s, 3H, CH_3(arom.)), 1.52 (s, 3H, CH_3), 1.46 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 138.53 (C arom.–CH_3), 135.69 (C4), 134.11 (C arom.–C4), 129.38 (C (Ho_{CH_3})), 126.00 (di, C (Hm_{CH_3})), 124.34 (C (H3)), 110.69 (C isopropylidene), 78.15 (C (H6)), 73.46 (C (H5)), 73.38 (C (H1)), 62.30 (C (H2)), 28.46 (CH_3), 26.07 (CH_3), 21.18 (CH_3(arom.)). IR (neat): 3452 (O–H, w), 2921 (C–H (CH_3), m), 2092 (N_3, s), 1256 (s), 1208 (C–N, m), 1059 (C–O–C, s), 875 (C–H, s), 804 (C=C, s). GC–MS: 287 (M^+-CH_3, 13), 273 (M^+-N_2, 6), 144 ($PhCH_2^+ + 2H_2O + CH_3$, 100), 105 ($PhCH_2^+ + CH_3$, 17), 91 ($PhCH_2^+$, 25), 77 (Ph, 17), 58 (C_3H_6O, 26), 43 ($N_2 + CH_3$, 56). TLC: R_f 0.47 (hexane/EtOAc, 70/30). HRMS: *m*/*z* calc. for $(C_{16}H_{19}N_3O_3Na)^+$: 324.1319. Found: 324.1318%.

4.1.4. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(2-(methyl)phenyl)cyclohex-3-ene-1-ol (**5d**)

^{1}H NMR ($CDCl_3$, 300 MHz) 7.26–7.17 (m, 4 H, Ph), 6.11 (bs, 1H, H3), 4.79 (d, J_{5-6} = 6.21, 1H, H5), 4.18 (dd, J_{6-5} = 6.96, J_{6-1} = 9.48, 1H, H6), 3.91 (d, J_{2-1} = 8.34, 1H, H2), 3.77 (t, J_{1-2} = 9.03, J_{1-6} = 9.50, 1H, H1), 2.88 (bs, 1H, OH), 2.31 (s, 3H, CH_3(arom.)), 1.56 (s, 3H, CH_3), 1.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 137.70 (C arom.–CH_3), 135.65 (C4 and C arom.–C4), 130.82 (C (H3)), 130.42, 128.47, 125.1 (Ph), 111.22 (C isopropylidene), 77.85 (C (H6)), 73.61 (C (H5)), 72.83 (C (H1)), 62.16 (C (H2)), 28.11 (CH_3), 25.86 (CH_3), 20.09 (CH_3(arom.)). ESI-MS: 324 ($(M+Na)^+$, 100), 259 ($M^+-CH_3-N_2$, 18), 201 (259.0–C_3H_6O, 46), 183 (201–H_2O, 23). This compound had identical chromatographic properties with the starting material and could no be isolated in the pure state.

4.1.5. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(4-(fluoro)phenyl)cyclohex-3-ene-1-ol (**5e**)

White solid. M.p.: 99–102 °C. $[\alpha]_D^{24}$ + 11.10 (*c* 0.45, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.53 (m, 2H, Hm_F), 7.04 (m, 2H, Ho_F), 5.99 (bs, 1H, H3), 4.98 (d, J_{5-6} = 5.46, 1H, H5), 4.19 (dd, J_{6-5} = 6.00, J_{6-1} = 8.94, 1H, H6), 4.07 (bd, J_{2-1} = 8.37, 1H, H2), 3.78 (bt, J_{1-2} = 8.25, J_{1-6} = 8.58, 1H, H1), 2.89 (bs, 1H, OH), 1.53 (s, 3H, CH_3), 1.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 162.90 (d, J_{CF} = 247, C arom.–F), 134.90 (C4), 133.17 (C arom.–C4), 127.98 (d, di, $^3J_{CF}$ = 8, C (Hm_F)), 125.31 (C (H3)), 115.91(d, di, $^2J_{CF}$ = 21, C (Ho_F)), 110.82 (C isopropylidene), 78.15 (C (H6)), 73.43 (di, C (H1) and C (H5)), 62.17 (C (H2)), 28.43 (CH_3), 26.07 (CH_3). IR (neat): 3465 (O–H, w), 2096 (N_3, s), 1229 (C–F, m), 1207 (C–N, m), 1062 (C–O–C, s), 979 (C–H, s), 875 (C=C, s). GC–MS: 207 (M^+-PhF, 10), 77 (Ph, 3), 58 (C_3H_6O, 35), 43 ($N_2 + CH_3$, 100). TLC: R_f 0.44 (hexane/EtOAc, 70/30). HRMS: *m*/*z* calc. for $(C_{15}H_{16}FN_3O_3Na)^+$: 328.1068. Found: 328.1066%.

4.1.6. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(4-(trifluoromethyl)phenyl)cyclohex-3-ene-1-ol (**5f**)

Brownish crystalline solid. M.p.: 118–119 °C. $[\alpha]_D^{24}$ + 12.7 (*c* 0.56, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.64 (m, 4 H, Ho_{CF_3} and Hm_{CF_3}), 6.13 (bs, 1H, H3), 5.02 (d, J_{5-6} = 6.00, 1H, H5), 4.23 (dd, J_{6-5} = 6.27, J_{6-1} = 9.03,

1H, H6), 4.11 (bd, $J_{2-1} = 8.97$, 1H, H2), 3.81 (t, $J_{1-2} = 9.09$, $J_{1-6} = 9.12$, 1H, H1), 2.80 (bs, 1H, OH), 1.54 (s, 3H, CH_3), 1.48 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 140.50 (C4), 135.01 (C arom.–C4), 130.47 (d, $^2J_{CF} = 33$, C arom.–CF_3), 127.58 (C (H3)), 126.58 (di, C (Hm_{CF_3})), 125.62 (d, di $^3J_{CF} = 4$, C (Ho_{CF_3})), 124.21 (q, $J_{CF} = 272$, CF_3), 110.98 (C isopropylidene), 78.07 (C (H6)), 73.41 (C (H5)), 73.22 (C (H1)), 62.04 (C (H2)), 28.37 (CH_3), 26.06 (CH_3). IR (neat): 3425 (O–H, w), 2124 (N_3, s), 1251 (C–F (CF_3), m), 1218 (C–N, m), 1068 (C–O–C, s), 876 (C–H, s), 820 (C=C, s). GC–MS: 229 (M^+-CF_3- C_3H_6O, 31), 209 (M^+-PhCF_3, 12), 145 ($PhCF_3$, 10), 101 ($CF_3 + H_2O + CH_3$, 46), 69 (CF_3^+, 17), 43 ($N_2 + CH_3$, 100). TLC: R_f 0.32 (hexane/EtOAc, 70/30). HRMS: m/z calc. for $(C_{16}H_{16}F_3N_3O_3Na)^+$: 378.1036. Found: 378.1034%.

4.1.7. (3S,4R,5R,6R)-4-(3-azido-4-hydroxy-5,6-O-(isopropylidenedioxy)cyclohex-1-enyl)benzaldehyde (**5g**)

Yellow solid. M.p.: 104–106 °C. $[\alpha]_D^{25} + 22.08$ (c 0.36, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) 10.02 (s, 1H, CHO), 7.89 (d, 2H, $J_{o-m} = 8.13$, Ho$_{CHO}$), 7.72 (d, 2H, $J_{m-o} = 8.19$, Hm$_{CHO}$), 6.20 (s, 1H, H3), 5.05 (d, $J_{5-6} = 6.03$, 1H, H5), 4.24 (dd, $J_{6-5} = 6.39$, $J_{6-1} = 8.91$, 1H, H6), 4.12 (d, $J_{2-1} = 10.20$, 1H, H2), 3.82 (t, $J_{1-2} = 9.06$, $J_{1-6} = 9.09$, 1H, H1), 2.84 (bs, 1H, OH), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 191.67 (CHO), 142.84 (C4), 136.06 (C arom.–C4), 135.12 (C–CHO arom.), 130.04 (di, C (Ho_{CHO})), 128.27 (C (H3)), 126.84 (di, C (Hm_{CHO})), 110.99 (C isopropylidene), 78.07 (C (H6)), 73.36 (C (H5)), 73.14 (C (H1)), 62.11 (C (H2)), 28.38 (CH_3), 26.09 (CH_3). IR (neat): 3461 (O–H, w), 2989 and 2923 (C–H (CHO)), 2095 (N_3, s), 1698 (C=O, s), 1258 (s), 1213 (C–N, m), 1060 (C–O–C, s), 877 (C–H, s), 811 (C=C, s). GC–MS: 282 (M^+-CH_3- H_2O, 4), 210 ($M^+-PhCHO$, 5), 182 ($M^+-C_3H_6O$–Ph, 3), 105 ($PhCO^+$, 4), 85 ($C_3H_6O + N_2$, 34), 77 (Ph, 4), 58 (C_3H_6O, 100), 51 ($C_4H_3^+$, 4), 43 ($N_2 + CH_3$, 77). TLC: R_f 0.28 (hexane/EtOAc, 70/30). HRMS: m/z calc. for $(C_{16}H_{17}N_3O_4Na)^+$: 338.1111. Found: 338.111%.

4.1.8. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidene-dioxy)-4-(thiophen-3′-yl)cyclohex-3-ene-1-ol (**5h**)

Brownish solid. M.p.: 98–100 °C. $[\alpha]_D^{25} + 32.24$ (c 0.56, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz) 7.46 (s, 1H, H2′), 7.26 (bs, 2 H, H4′ and H5′), 6.03 (s, 1H, H3), 4.96 (d, $J_{5-6} = 6.00$, 1H, H5), 4.17 (t, $J_{6-5} = 6.48$, $J_{6-1} = 8.73$, 1H, H6), 4.06 (d, $J_{2-1} = 8.88$, 1H, H2), 3.76 (t, $J_{1-2} = 9.09$, $J_{1-6} = 9.18$, 1H, H1), 2.78 (bs, 1H, OH), 1.54 (s, 3H, CH_3), 1.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 138.61(C4), 131.11 (C heteroarom.–C4), 126.09 (C (H4′)), 125.03 (C (H5′)), 123.91 (C (H3)), 122.94 (C (H2′)), 110.81 (C isopropylidene), 78.12 (C (H6)), 73.79 (C (H5)), 73.59 (C (H1)), 62.15 (C (H2)), 28.46 (CH_3), 26.13 (CH_3). IR (neat): 3446 (O–H, w), 2095 (N_3, s), 1257 (s), 1207 (C–N, m), 1056 (C–O–C, s), 866 (C–H, s), 777 (C=C, s), 752 (C–H (C_4H_4S, m)). GC–MS: 293 (M^+, 8), 193 ($M^+-C_3H_6O-N_3$, 22), 136 ($C_4H_4S + CH_3$, 34), 43 ($N_2 + CH_3$, 100). TLC: R_f 0.53 (hexane/EtOAc, 70/30). HRMS: m/z calc. for $(C_{13}H_{15}N_3O_3SNa)^+$: 316.0726. Found: 316.0729%.

4.1.9. (1R,2S,5R,6R)-2-azido-5,6-O-(isopropylidenedioxy)-4-(thiophen-2′-yl)cyclohex-3-ene-1-ol (**5i**)

^1H NMR ($CDCl_3$, 300 MHz) 7.24 (m, 2H, H3′ and H4′), 7.00 (bs, 1H, H5′), 6.02 (bs, 1H, H3), 4.97 (d, $J_{5-6} = 5.88$, 1H, H5), 4.16 (dd, $J_{6-5} = 6.30$, $J_{6-1} = 9.09$, 1H, H6), 4.07 (d, $J_{2-1} = 8.91$, 1H, H2), 3.76 (t, $J_{1-2} = 9.15$, $J_{1-6} = 9.57$, 1H, H1), 2.78 (bs, 1H, OH), 1.55 (s, 3H, CH_3), 1.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) 140.96 (C4), 130.81 (C heteroarom.–C4), 130.51 (C (H2′)), 127.68 (C (H5′)), 125.89 and 125.81 (C (H3′ and H4′)), 123.42 (C (H3)), 110.92 (C isopropylidene), 78.06 (C (H6)), 73.67 (C (H5)), 73.53 (C (H1)), 62.16 (C (H2)), 28.42 (CH_3), 26.09 (CH_3). ESI-MS: 316 ($(M+Na)^+$, 44), 251 (M^+-N_3, 100), 193 (251–C_3H_6O, 89). This compound had identical chromatographic properties with the starting material and could no be isolated in the pure state.

Acknowledgements

The following organizations contributed to support this work: CNPq and FAPESP for financial support. A.B. is grateful to PEDECIBA and DINACYT for a Doctoral Fellowship. MestreNova generously granted a license for the use of its NMR processing software.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.01.006.

References

[1] (a) G.A. Molander, R. Figueroa, Aldrichim. Acta 38 (2005) 49;
(b) G.A. Molander, N. Ellis, Acc. Chem. Res. 40 (2007) 275;
(c) H.A. Stefani, R. Cella, A. Vieira, Tetrahedron 63 (2007) 3623;
(d) S. Darses, J.P. Genêt, Eur. J. Org. Chem. (2003) 4313.
[2] (a) E. Vedejs, R.W. Chapman, S.C. Fields, S. Lin, M.R. Schrimpf, J. Org. Chem. 60 (1995) 3020;
(b) E. Vedejs, S.C. Fields, R. Hayashi, S.R. Hitchcock, D.R. Powell, M.R. Schrimpf, J. Am. Chem. Soc. 121 (1999) 2460.
[3] (a) T. Hudlicky, D. Gonzalez, D.T. Gibson, Aldrichim. Acta 32 (1999) 35;
(b) M.G. Banwell, A.J. Edwards, G.J. Harfoot, K.A. Jolliffe, M.D. McLeod, K.J. McRae, S.G. Stewart, M. Vogtle, Pure Appl. Chem. 75 (2003) 223.
[4] (a) T. Hudlicky, Chem. Rev. 96 (1996) 3;
(b) T. Hudlicky, J. Braz. Chem. Soc. 9 (1998) 313;
(c) T. Hudlicky, Arkivoc (2006) 276;
(d) T. Hudlicky, D.A. Entwistle, K.K. Pitzer, A. Thorpe, J. Chem. Rev. 96 (1996) 1195.
[5] (a) M.G. Banwell, J.K. Okanya, A.C. Willis, Org. Lett. 9 (2007) 3503;

(b) M.G. Banwell, K.A.B. Austin, A.C. Willis, Tetrahedron 63 (2007) 6388;
(c) K.A.B. Austin, M.G. Banwell, D.T.J. Loong, A.D. Rae, A.C. Willis, Org. Biomol. Chem. 3 (2005) 1081;
(d) M.G. Banwell, A.J. Edwards, D.T.J. Loong, Arkivoc (2004) 53.
[6] (a) H.A.J. Carless, Y. Dove, Tetrahedron: Asymmetry 7 (1996) 649;
(b) C.R. Johnson, B.A.J. Johns, Org. Chem. 62 (1997) 6046;
(c) C. Sanfilippo, A. Patti, M. Piattelli, G. Nicolosi, Tetrahedron: Asymmetry 9 (1998) 2809.
[7] C. Vitelio, A. Bellomo, M. Brovetto, G. Seoane, D. Gonzalez, Carbohydr. Res. 339 (2004) 1773.
[8] A. Bellomo, C. Giacomini, B. Brena, G. Seoane, D. Gonzalez, Synth. Commun. 37 (20) (2007) 3509.
[9] (a) A. Bellomo, D. Gonzalez, Tetrahedron: Asymmetry 17 (2006) 474;
(b) A. Bellomo, D. Gonzalez, Tetrahedron Lett. 48 (2007) 3047.
[10] M. Mandel, T. Hudlicky, J. Chem. Soc., Perkin Trans. 1 (1993) 741.
[11] H. Yoshizaki, J.E. Bäckvall, J. Org. Chem. 63 (1998) 9339.
[12] (a) A. Dondoni, Chem. – An Asian J. 2 (2007) 700;
(b) M.V. Gil, M.J. Arévalo, O. Lopez, Synthesis (2007) 1589.
[13] (a) R. Cella, R.L.O.R. Cunha, A.E.S. Reis, D.C. Pimenta, C.F. Klitzke, H.A. Stefani, J. Org. Chem. 71 (2006) 244;
(b) H.A. Stefani, R. Cella, Tetrahedron 62 (2006) 5656;
(c) H.A. Stefani, R. Cella, F.A. Dörr, C.M.P. Pereira, G. Zeni, M. Gomes Jr., Tetrahedron Lett. 46 (2005) 563;
(d) R. Cella, A.T.G. Orfão, H.A. Stefani, Tetrahedron Lett. 47 (2006) 5075.
[14] (a) G.A. Molander, M.R. Rivero, Org. Lett. 4 (2002) 107;
(b) G.A. Molander, C.M. Bernardi, J. Org. Chem. 67 (2002) 8424;
(c) G.A. Molander, L.A. Felix, J. Org. Chem. 70 (2005) 3950;
(d) G.A. Molander, T. Fumagalli, J. Org. Chem. 71 (2006) 5743.
[15] (a) D. Gonzalez, T. Martinot, T. Hudlicky, Tetrahedron Lett. 40 (1999) 3077;
(b) B.A. Johns, C.R. Johnson, Tetrahedron Lett. 39 (1998) 749.
[16] G.A. Molander, B.W. Katona, F. Machrouhi, J. Org. Chem. 67 (2002) 8416.
[17] A. Suzuki, J. Organomet. Chem. 576 (1999) 147.
[18] G.A. Molander, M.D. Elia, J. Org. Chem. 71 (2006) 9198.
[19] (a) D.N. Korolev, N.A. Bumagin, Tetrahedron Lett. 47 (2006) 4225;
(b) I. Kondolff, H. Doucet, M. Santelli, Tetrahedron 60 (2004) 3813.
[20] (a) R. Cella, R.L.O.R. Cunha, A.E.S. Reis, D.C. Pimenta, C.F. Klitzke, H.A. Stefani, J. Org. Chem. 71 (2006) 244;
(b) H.A. Stefani, R. Cella, A. Vieira, Tetrahedron 63 (2007) 3623.
[21] R. Barbiéri, A.C. Massabni, C.R. Bellato, Química Nova 14 (3) (1991) 212.