Tetrahedron: *Asymmetry* 21 (2010) 2899–2903

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Efficient kinetic resolution of (±)-1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol with the lipase B of *Candida antarctica*

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ARTICLE INFO

Article history:
Received 30 September 2010
Accepted 2 December 2010
Available online 11 January 2011

ABSTRACT

(±)-1,2-*O*-Isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol is a relevant starting material in the synthesis of inositol phosphates and their analogs. In this study, we disclose our efforts toward an efficient methodology for the kinetic resolution of this compound by lipase B of *Candida antarctica* (Novozym 435). This reaction selectively affords L-(−)-1,2-*O*-isopropylidene-5-*O*-acetyl-3,6-di-*O*-benzyl-*myo*-inositol. From a conversion of 34% with EtOAc as an acylating agent, the use of vinyl acetate increased the yield to over 49%, while maintaining a very high ee (>99%). The combination of the latter reagent with TBME as a solvent accelerates the reaction.

1. Introduction

Chiral *myo*-inositol derivatives, such as d-1,4,5-*myo*-inositol trisphosphate, play key roles in cellular signal transductions.[1] For this reason, such substances are important tools in cell biology investigations. Moreover, inositols hold promise in the development of drugs.

myo-Inositol itself, an accessible achiral substance, is the most used precursor for its chiral derivatives. As this strategy implies the formation of racemic intermediates, resolution is commonly required. It is noteworthy that most routes for the enantioselective synthesis still rely on the resolution by derivatization (formation of diastereomers).[1–3] Although these strategies are effective, the need of steps for the introduction and removal of the chiral auxiliary naturally makes them even more costly.

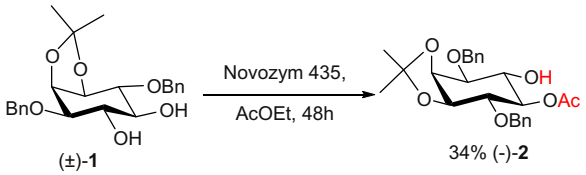
The use of enzymes in synthesis, especially lipases, is very attractive due to the possibility of engaging unnatural substrates in highly selective and efficient reactions catalyzed by these biocatalysts. Moreover, such transformations can be run under mild conditions.[4]

Despite the clear potential, lipases have not been well explored in the chemoenzymatic syntheses of *myo*-inositols.[5]

We have recently found that racemic (±)-1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-*myo*-inositol (±)-**1** (Scheme 1), despite its steric hindrance, could be resolved by a lipase.[6] Substance (±)-**1**[7,8] is a relevant precursor of biologically active *myo*-inositol derivatives.[9]

Thus, the lipase B of *Candida antarctica* (Novozym 435) converted diol (±)-**1** into monoacetate (−)-**2** in 34% yield and >99% ee.[6] The acylation was found to be highly regioselective, occurring at the C-5 hydroxyl group. Based on this preliminary result, theoretical models were developed for the rationalization of the observed regio- and enantioselectivities. To the best of our knowledge, no such bulky *myo*-inositol derivative bearing two types of protecting group, such as (±)-**1**, has previously been employed as a substrate for lipases.

This result encouraged us to improve this kinetic resolution. Herein, we report the results of this investigation. We also disclose the synthesis of (±)-**2**, which streamlined the determination of the enantiomeric excess of (−)-**2**.



Scheme 1. Kinetic resolution of (±)-**1** catalyzed by Novozym 435 in AcOEt.

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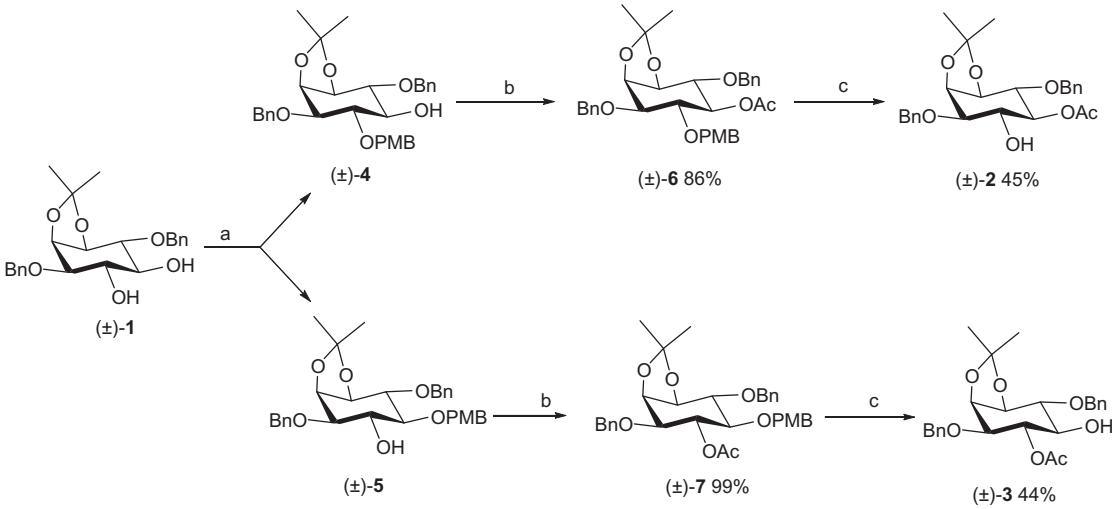
doi:10.1016/j.tetasy.2010.12.006



Scheme 2. Synthesis of (±)-**2** and regiosomer (±)-**3**: Reagents and conditions (a) (i) Bu_2SnO, MeOH/PhMe 1:1, 100 °C, 3 h; (ii) PMBBr, TBAB, DIPEA, PhMe, 100 °C, 11 h, 81% (**4**:**5** ratio = 63:37, by ^1H NMR); (b) DMAP, Ac_2O, pyridine, 0 °C→rt, overnight; (c) DDQ, CH_2Cl_2/H_2O 9:1, 0 °C→rt, 2 h.

2. Results and discussion

2.1. Synthesis of (±)-2

The direct acylation of (±)-**1** with Ac_2O by the usual procedure under controlled conditions (Et_3N, DMAP, CH_2Cl_2, −20 °C) afforded a roughly 1:1 mixture of monoacetates, along with a minor amount of the diacetate derivative. The monoacetates in such a mixture were not separable by chromatography (silica gel). Thus, we devised the chemical synthesis of (±)-**2** from (±)-**1** (Scheme 2). This substance was monoprotected with PMBBr via the stannylene derivative[7,10] affording a mixture of regioisomeric mono-PMB ethers **4** and **5,** which were then separated. The ^1H NMR spectra of these compounds were correlated with those of the known tri-benzyl ethers **8** and **9**, respectively (Fig. 1), indicating that the protection occurred as shown. Triether **5** was then acetylated and then the PMB group was cleaved by DDQ,[11,12] leading to desired hydroxyacetate (±)-**2**. Regioisomer **3** was prepared in a similar manner. The NMR spectra of (±)-**2** and (±)-**3** confirmed the previous structural assignment of (−)-**2** by 2D-NMR experiments.[6]

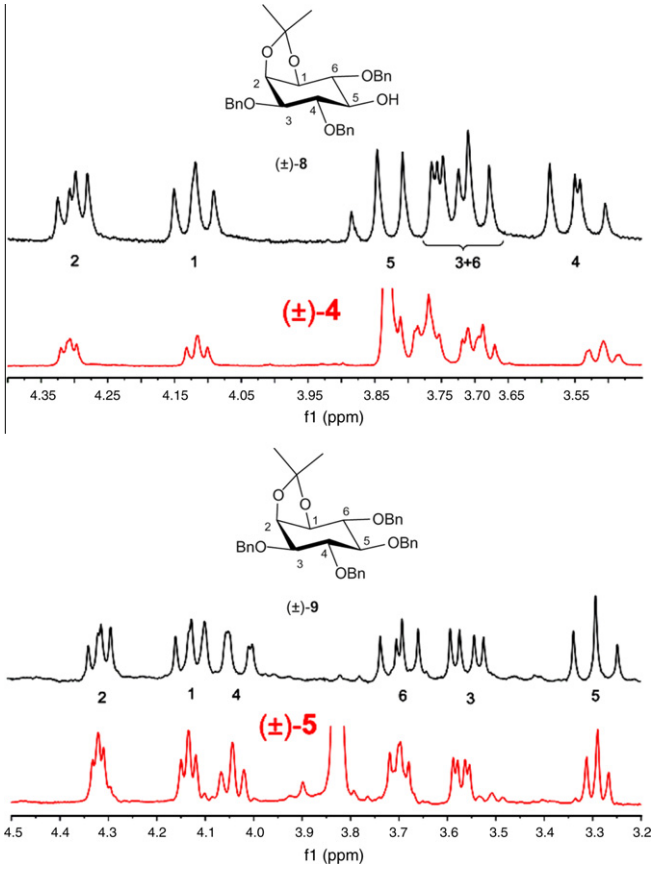


Figure 1. Comparison of NMR (400 MHz, $CDCl_3$) data of (±)-**4** and (±)-**5** to those of corresponding tribenzyl ethers (±)-**8** and (±)-**9**.

2.2. Solvent selection for the resolution of (±)-1 by Novozym 435

An investigation into the effect of solvents on the performance of the resolution of (±)-**1** (acylation with EtOAc) catalyzed by Novozym 435 was carried out. The conditions for determining the ee (Fig. 2, see Section 4) and configuration of (−)-**2** were established in a previous work.[6] It is known that the solvent affects both enzyme activity and selectivity in the complex mechanism involving interactions among the enzyme, the substrate (ligand) and the reaction medium. The literature has already shown a strong solvent influence on enantioselectivity.[13,14] The choice of toluene,

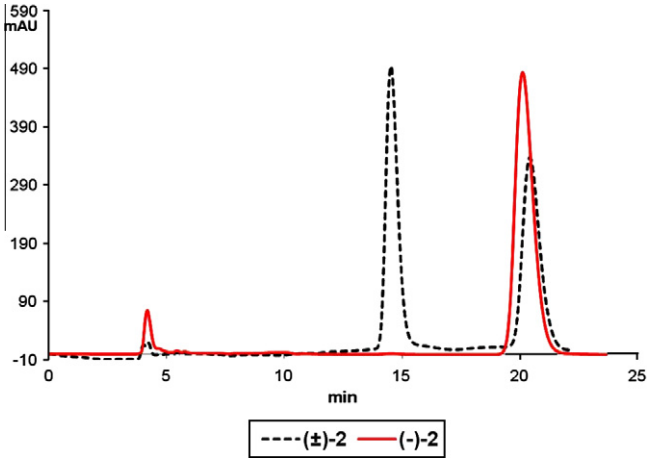


Figure 2. HPLC analysis of (−)-**2** and (±)-**2** (see Section 4).

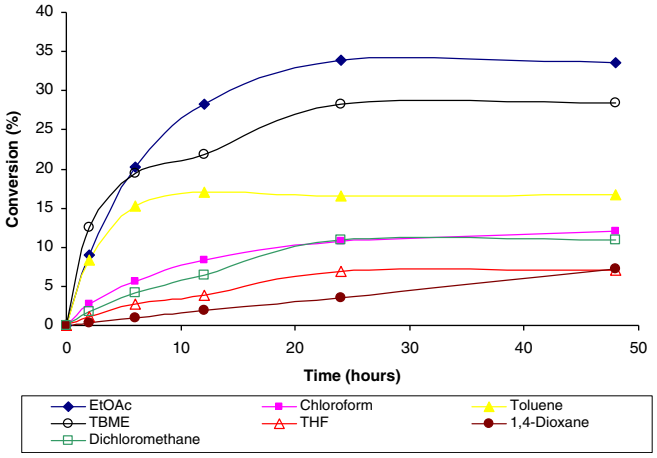


Figure 3. Time course of conversion in the resolution of (±)-**1** with EtOAc catalyzed by Novozym 435 in different solvents.

TBME (*tert*-butyl methyl ether), $CHCl_3$, CH_2Cl_2, THF, 1,4-dioxane, and EtOAc as solvents in our assays took into account both the substrate solubility and the stability of that commercial enzyme. The progress of the resolution reactions catalyzed by lipase in such media was investigated (Fig. 3).

We found that the more hydrophobic solvents enhanced the conversion rate in the resolution of (±)-**1**. The initial rates were higher in toluene (0.206 μmol min^{-1} g^{-1}) and TBME (0.602 μmol min^{-1} g^{-1}). Lower rates were observed when less hydrophobic solvents were employed: $CHCl_3$ (0.060 μmol min^{-1} g^{-1}) CH_2Cl_2 (0.042 μmol min^{-1} g^{-1}), THF (0,028 μmol min^{-1} g^{-1}) and 1,4-dioxane (0.006 μmol min^{-1} g^{-1}). Conversions to acetate (−)-**2** followed this trend (Table 1). The more hydrophilic solvents arguably remove the H_2O molecules bound to the enzyme surface, which modifies its structure. The result of this is a change in activity and enantioselectivity.[15] However, the reaction in EtOAc, a more hydrophilic solvent as well, showed high initial rates (0.468 μmol min^{-1} g^{-1}) and conversions (after 24 h). In this case, as the solvent itself is the acylating agent, it led to an equilibrium shift in favor of (−)-**2** formation.

High ee (>99%) and enantioselectivity (E >100) were obtained in all cases (Table 1). The conversion degree was not improved upon when AcOEt was used as the acylating agent.

2.3. Acylating agent selection for the resolution of (±)-1 by Novozym 435

As acylations catalyzed by lipases involve the formation of an acyl-enzyme intermediate, the nature of the acylating agent has a strong effect on the enzyme activity. The use of vinylic esters as these reagents has the advantage of forming carbonyl by-products, instead of alcohols, which makes those reactions irreversible. It also results in higher conversion rates.[16,17] Thus, we studied the effect of the replacement of AcOEt, as a solvent and/or an acylating agent, with either vinyl acetate or isopropenyl acetate with the resolution of (±)-**1**. We sought higher efficiency in these reactions, meaning high conversions to (−)-**2**, while maintaining its high ee. As TBME had previously performed well, we also assayed combinations of this solvent with the acylating agents.

Table 1
Conversion (c), enantiomeric excess (ee) and enantioselectivity (E) in the resolution of (±)-**1** with EtOAc in different solvents by Novozym 435

Solvent	(±)-**1**			
	Time (h)	c (%)	ee_p (%)	E
EtOAc	24	33.6	>99	>100
TBME	24	28.3	>99	>100
Toluene	12	16.7	>99	>100
Chloroform	48	12.0	>99	>100
Dichloromethane	24	11.0	>99	>100
THF	24	7.1	>99	>100
1,4-Dioxane	48	7.2	>99	>100

Table 2
Conversion (c), enantiomeric excess (ee) and enantioselectivity (E) in the resolution of (±)-1 with different acylating agents by Novozym 435

Acylating agent	Solvent	(±)-**1** Time (h)	c (%)	ee_p (%)	E
Vinyl acetate	TBME	24	48.0	>99	>100
	Vinyl acetate	48	49.9	>99	>100
Isopropenyl acetate	TBME	24	43,8	>99	>100
	Isopropenyl acetate	48	45.3	>99	>100
EtOAc	TBME	24	28.3	>99	>100
	EtOAc	24	33.6	>99	>100

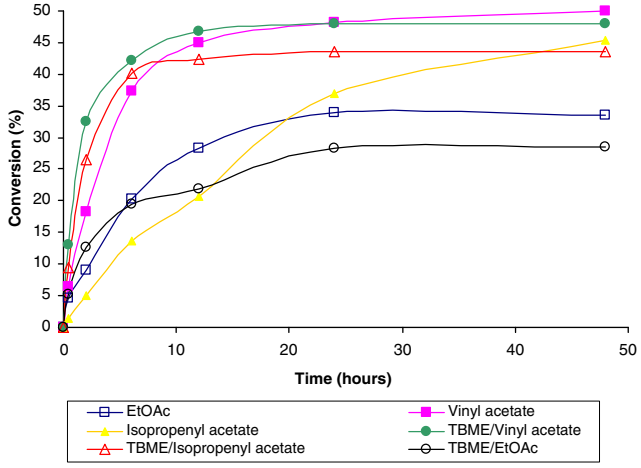


Figure 4. Time course of conversion in the resolution of (±)-**1** catalyzed by Novozym 435 in different acylating agents.

As expected, alkenyl acetates performed much better than EtOAc (Table 2, Fig. 4). The use of vinyl and isopropenyl acetate led to higher conversions, with vinyl acetate affording the best results. The ee of (−)-**2** remained high in these cases. The use of TBME as solvent, along with the same reagents, brought about higher rates. Conversions were not as high as in the reaction with vinyl acetate as solvent. Thus, our data demonstrate that both the d and l [in the form of l-(-)-**2**] enantiomorphs of **1** may be obtained in high ee.

3. Conclusion

We have disclosed the conditions for a very efficient kinetic resolution of racemic *myo*-inositol derivative **1** with Novozym 435. This compound is a relevant precursor of inositol derivatives. The use of vinyl acetate as an acylating agent enabled high conversion to monoester (−)-**2** while maintaining high enantioselectivity. Moreover, the use of TBME as a solvent in combination with vinyl acetate proved to be an alternative condition.

4. Experimental

4.1. Resolution of (±)-1

The enzymatic reactions were realized in closed thermostatized flasks containing (±)-**1** (5 mg), acylating agent (1.0 mL), and

Novozym 435 (50 mg) in the solvent (1.5 mL) at 30 °C. Aliquots were taken after 0.5, 2, 6, 12, 24, and 48 h and analyzed by HPLC. The physical data of product L-(−)-**2** were reported in the previous work:[6] $[\alpha]_D = -8.1$ (*c* 0.65, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$), δ 1.37 (s, 3H), 1.53 (s, 3H), 2.10 (s, 3H), 3.68–3.75 (m, 2H), 4.05 (t, 1H, *J* = 8.65 Hz), 4.24 (t, 1H, *J* = 6.01 Hz), 4.42 (dd, 1H, *J* = 3.62 5.97 Hz), 4.70–4.84 (m, 4H), 4.89 (t, 1H, *J* = 8.22 Hz), 7.28–7.41 (m, 10H). ^{13}C NMR (100.62 MHz, $CDCl_3$), δ 21.1, 25.4, 27.4, 70.4, 72.8, 72.9, 73.5, 75.2, 76.9, 78.5, 79.0, 106.5, 127.6, 127.7, 128.1, 128.3, 128.6, 137.8, 138.1, 171.0. EM-ESI: *m/z* = 465.1 $[M+Na]^+$.

4.2. HPLC analysis of conversion of (±)-1 to (−)-2

Conversion analyses were done via HPLC on a Shimadzu-C18 column (40 °C in a CTO-20A oven) eluted with an acetonitrile–H_2O (60:40) mixture (0.5 mL/min) by a Shimadzu LC-20AT pump. A Shimadzu SPD-M20A variable-wavelength UV/vis detector was employed, with the detection set at 215 nm, and the Shimadzu LCsolution software was used for chromatogram integration. The samples to be analyzed were filtered through a 0.45 μm PTFE filter. The retention times of the substrate (±)-**1** and product L-**2** were 9.3 min and 15.4 min, respectively.

4.3. Determination of ee and *E*

Chromatographic determinations of the enantiomeric excesses (ee) of L-(−)-**2** were carried out on the same equipment mentioned above using a Chiralcel OD-H column (5 μm; 4.6 × 250 mm) eluted with a 9:1 hexane–2-propanol (0.8 mL/min). Retention times of the enantiomers: D-**2** (15.7 min), L-**2** (22.3 min).

The enantiomeric ratio *E* was calculated by using the equation of Chen et al.[18] as given below:

$$E = \frac{\ln[1 - c(1 + ee_p)]}{\ln[1 - c(1 - ee_p)]} \quad (1)$$

where

$$C = \frac{[P] + [Q]}{[A]_0 + [B]_0} = \text{extent of conversion} \quad (2)$$

$$ee_p = \frac{[P] - [Q]}{[P] + [Q]} = \text{enantiomeric purity of product P} \quad (3)$$

where A and B stand for substrate, and P and Q are products, respectively.

4.4. Physical data

4.4.1. (±)-1,2-*O*-Isopropylidene-5-*O*-acetyl-3,6-di-*O*-benzyl-*myo*-inositol (±)-2

At first, DDQ (0.197, 0.868 mmol) was added in 3 portions every 30 min to PMB-ether (±)-**6** (0.202 g, 0.114 mmol) dissolved in a stirred 9:1 CH_2Cl_2/H_2O mixture (2.0 mL), the first one at 0 °C. After 2 h from the start, the reaction mixture was cooled again to 0 °C and a satd aq $NaHCO_3$ soln (10 mL) was added. After 5 min, the resulting mixture was warmed to rt and the product was extracted with CH_2Cl_2 (40 mL). The organic phase was washed with distilled H_2O (20 mL) twice, dried over Na_2SO_4 and filtered. The volatiles were evaporated under vacuum and the resulting residue was purified by flash chromatography (elution with ethyl acetate/hexane mixtures) leading to (±)-**2** (0.0471 g; 45%). IR (KBr) ν_{max} cm^{-1} 3524, 3448 (b), 2976, 2931, 2915, 1724 (F), 1638, 1498, 1454, 1379, 1367, 1253, 1241, 1217, 1151, 1109, 1061, 1029, 874, 731, 696; ^1H NMR (400 MHz, $CDCl_3$), δ 1.37 (s, 3H), 1.53 (s, 3H), 2.10 (s, 3H), 2.81 (1OH, b), 3.67–3.75 (m, 2H), 4.04 (t, 1H, *J* = 8.7 Hz), 4.23 (t, 1H, *J* = 6.0 Hz), 4.41 (dd, 1H, *J* = 3.85 5.4 Hz), 4.70–4.83 (m, 4H), 4.89 (t, 1H, *J* = 8.3 Hz), 7.29–7.41 (m, 10H). ^{13}C NMR (100.62 MHz, $CDCl_3$), δ 21.1, 25.4, 27.4, 70.4, 72.8, 72.9, 73.5, 75.3, 77.0, 78.5, 79.1, 106.5, 127.6, 127.7, 128.1, 128.3, 128.6, 137.8, 138.1, 171.0; Anal. Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found: C, 68.05; H, 6.64.

4.4.2. (±)-1,2-*O*-Isopropylidene-4-*O*-acetyl-3,6-di-*O*-benzyl-*myo*-inositol (±)-3

The procedure in Section 4.4.1 was followed in the reaction of (±)-**7** (0.012 g) to afford (±)-**3** (0.0049 g; 44%) ^1H NMR (400 MHz, $CDCl_3$), δ 1.38 (s, 3H), 1.56 (s, 3H), 2.11 (s, 3H), 3.58 (t, 1H, *J* = 8.1 Hz), 3.73–3.81 (m, 2H), 4.22 (td, 1H, *J* = 1.9 6.2 Hz), 4.37–4.39 (m, 1H), 4.67–4.92 (m, 4H), 5.28 (td, 1H, *J* = 1.5 8.0 Hz), 7.28–7.40 (m, 10H).

4.4.3. (±)-1,2-*O*-Isopropylidene-3,6-di-*O*-benzyl-4-O-(4′-methoxybenzyl)-*myo*-inositol (±)-4 and (±)-1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-5-O-(4′-methoxybenzyl)-*myo*-inositol (±)-5

At first, Bu_2SnO (0.066 g; 0.26 mmol) and diol (±)-**1** (0.101 g; 0.25 mmol) in a 1:1 toluene/CH_3OH mixture (4.0 mL) under stirring and Ar were heated to 100 °C for 3 h. Additional dry toluene (5.0–10.0 mL) was added and evaporated to dryness once more under vacuum. The residue had the trace amounts of solvent removed under high vacuum (40 min) and to this material, TBAB (0.048 g; 0.15 mmol), toluene (21.0 mL), and PMBBr (0.08 mL; 0.56 mmol) were added sequentially. Then, the resulting mixture was stirred at 120 °C for 11 h. Next, the volatiles were partially removed under vacuum and the obtained mixture was subjected directly to flash chromatography (elution with ethyl acetate/hexane mixtures). This yielded (±)-**4** and (±)-**5** and a mixture of both compounds (0.106 g combined; 81%, (±)-**4**/(±)-**5** = 63:37, by ^1H NMR). Compound (±)-**4:** IR (KBr) ν_{max} cm^{-1} 3467 (b), 3051, 3031, 2936, 2908, 2877, 2837, 1613, 1586, 1514, 1455, 1381, 1371, 1302, 1248, 1218, 1112, 1083, 1065, 1029, 868, 821, 738, 699; ^1H NMR (400 MHz, $CDCl_3$), δ 1.38 (s, 3H), 1.53 (s, 3H), 2,66 (1OH, b), 3.51 (t, 1H, *J* = 9,78 Hz), 3.67–3.72 (m, 2H), 3.75–3.81 (several signals, 6H, impurity), 3.83 (s, 3H), 4.12 (t, 1H, *J* = 6.23 Hz), 4.31 (dd, 1H, *J* = 4.04 5.38 Hz), 6.89–6.93 (m, 2H), 7.28–7.39 (m, 12H). Compound (±)-**5:** IR (KBr) ν_{max} cm^{-1} 3464 (l), 3063, 3031, 2988, 2935, 2908, 2879, 2837, 1613, 1586, 1514, 1497, 1455, 1381, 1371, 1302, 1248, 1219, 1173, 1111, 1084, 1066, 1035, 868, 822, 738, 699; ^1H NMR (400 MHz, $CDCl_3$), δ 1.36 (s, 3H), 1.50 (s, 3H), 2,63 (1OH, b), 3.29 (t, 1H, *J* = 9.04 Hz), 3.57 (dd, 1H, *J* = 3.55 9.66 Hz), 3.70 (dd, 1H, *J* = 6.85 8.80 Hz), 3.82 (s, 3H), 4.04 (t, 1H, *J* = 9.42 Hz), 4.13 (t, 1H, *J* = 6.48 Hz), 4.32 (t, 1H, *J* = 4.40 Hz), 4.64–4.94 (m, 6H), 6.87–6.93 (m, 2H), 7.28–7.44 (m, 12H).

4.4.4. (±)-1,2-*O*-Isopropylidene-4-*O*-acetyl-3,6-di-*O*-benzyl-5-O-(4′-methoxybenzyl)-*myo*-inositol (±)-6

A stirred solution of compound (±)-**4** (0.167 g; 0.321 mmol) and DMAP (0.079 g; 0,064 mmol) in pyridine (30 mL) under Ar was cooled to 0 °C and treated with Ac_2O (0.25 mL; 2.650 mmol). After 15 min, the reaction mixture was allowed to warm to rt. Then, a satd aq $NaHCO_3$ soln (10 mL) was added to the mixture at 0 °C. After 5 min, the resulting mixture was allowed to warm back to rt. The product was isolated (AcOEt as solvent) and purified according the usual procedure (see Section 4.4.1), yielding (±)-**6** (0.156 g; 86%). IR (KBr) ν_{max} cm^{-1} 3479 (b), 3064, 3032, 2989, 2936, 2908, 2885, 2838, 1743 (w), 1613, 1586, 1514, 1455, 1380, 1371, 1302, 1246, 1219, 1173, 1158, 1084, 1073, 1029, 868, 822, 738, 698; ^1H NMR (400 MHz, $CDCl_3$), δ 1.38 (s, 3H), 1.55 (s, 3H), 1.99 (s, 3H), 3.72 (dd, 1H, *J* = 6.5 8.6 Hz), 3.80–3.83 (m, 4H), 3.90 (t, 1H, *J* = 8.3), 4.19 (t, 1H, *J* = 6.11), 4.35 (dd, 1H, *J* = 3.7 5.7 Hz), 4.60–4.84 (m, 6H), 5.03 (t, 1H, *J* = 8.3 Hz), 6.88–6.90 (m, 2H), 7.23–7.40 (m, 12H).

4.4.5. (±)-1,2-*O*-Isopropylidene-5-*O*-acetyl-3,6-di-*O*-benzyl-4-*O*-(4′-methoxybenzyl)-*myo*-inositol (±)-7

The procedure in Section 4.4.4 was followed in the reaction of (±)-**5** (0.033 g) to afford (±)-**7** (0.0397g; 99%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.35 (s, 3H), 1.51 (s, 3H), 1.97 (s, 3H), 3.40 (t, 1H, J = 8.6 Hz), 3.66 (dd, 1H, J = 3.6 8.4 Hz), 4.52–4.84 (m, 6H), 5.42 (t, 1H, J = 8.4 Hz), 6.82–6.84 (m, 2H), 7.17–7.35 (m, 12H).

Acknowledgments

FAPERJ and CNPq for funding; CAPES for fellowship (AATS); Central Analítica/NPPN and CNRMN/IBM for NMR data; Laboratório de Síntese Orgânica Ambiental (IQ-UFRJ) for polarimetric analysis.

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