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Synthesis of 2-amino-1,3-diols incorporating the cyclobutane ring

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ABSTRACT

The synthesis of free and protected 2-amino-1,3-diols with threoninol substructure that incorporate a conformational restriction defined by the cyclobutane ring is reported. The key step in the synthesis of these target compounds, namely *cis*- and *trans*-c_4-threoninols, is the addition of methylmagnesium bromide to a cyclobutanone derivative. The selectivity of the reaction is modulated by the solvent.

1. Introduction

In the last few years, the synthesis of cyclobutane compounds has received great attention, due to their use as building blocks for the preparation of natural products. Moreover, the development of new synthetic strategies has allowed an easy access to this kind of rings.[1] In this context, a number of cyclobutane-containing derivatives such as cyclobutane-constrained α-amino acids,[2a,b] cyclobutane-constrained β-amino acids,[2c] cyclobutane peptide-turned mimics[2d] or cyclobutane nucleoside analogues[2e] have been reported recently in the literature.

Threoninol, a 2-amino-1,3-diol derivative, is an important compound obtained by reduction of the natural amino acid threonine (Thr) (Fig. 1). It has been proved to have some interesting applications. Thus, some conveniently protected derivatives could be used as analogues of ribonucleotides and modification of their structure would provide a library of compounds.[3] In nanomaterial chemistry, both the enantiomers of threoninol were used as linkers between DNA chains. The use of each enantiomer afforded the corresponding handed helix of DNA clusters.[4] On the other hand, somatostatin is a tetradecapeptide involved in very important biological processes. The receptors of this peptide are found to be expressed in 90% of carcinoid tumours. In terms of activity, octreotide is a somatostatin analogue more effective than somatostatin itself, due to a longer half life in vivo. Remarkably, threoninol is present in octreotide along with other D-amino acids.[5]

We intend to focus the attention on the 2-amino-1,3-diols and the development of new related structures. As part of our research program,[6,7] we have synthesized different cyclobutane derivatives,[6a,b] and wish to extend this work to the preparation of restricted 2-amino-1,3-diols containing the cyclobutane substructure. Particularly, it is our purpose to develop a new route for the synthesis of cis- and trans-stereoisomers of 2-amino-2-(hydroxymethyl)-1-methylcyclobutanol, abbreviated as c_4-threoninol and c_4-*allo*-threoninol, *trans*-**1** and *cis*-**1**, respectively (Fig. 1).

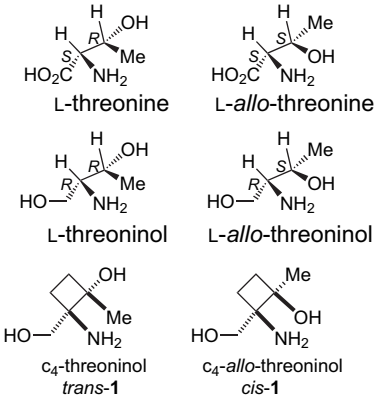

Figure 1. Threoninols and their cyclobutane derivatives.

The synthetic methodology that allows an easy formation of the cyclobutane ring involves the reaction of methyl 2-acetamidoacrylate **2** with ketene diethyl acetal **3** in a formal [2+2] cycloaddition. In this way, a tandem Michael–Dieckmann-type process gives compound **4**, which is then transformed into the versatile intermediate **5** (Scheme 1).[7] We have planned to obtain c_4-threoninols from **5**, by using methylmagnesium bromide to incorporate the methyl group into the position 2 of the cyclobutane ring (Scheme 2).

2. Results and discussion

As planned, the cyclobutane derivatives with threoninol substructure were easily achieved from **5**, by reaction with methylmagnesium bromide in different solvents and at different temperatures. This kind of reaction has been extensively studied.[8]

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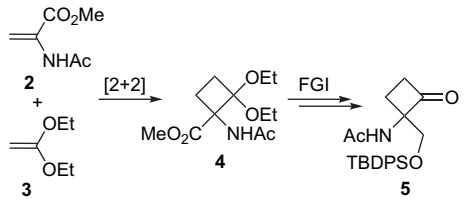
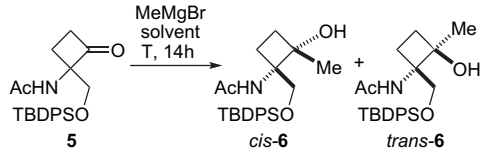


Scheme 1. Starting material for the preparation of c_4-threoninol derivatives (TBDPS=tertbutyldiphenylsilyl).



Scheme 2. Addition of methylmagnesium bromide to compound **5**.

More particularly, Pérez-Ossorio et al. described the addition of phenylmagnesium bromide to 3-phenylbutanone in different solvents at 30 °C.[8d] A linear correlation between stereoselectivity and the $E_T(30)$ parameter of the solvent was found. Similarly, the same trend could be identified in the experiments carried out under our conditions (Scheme 2 and Table 1). Thus, when the addition of methylmagnesium bromide to **5** takes place in THF, dimethoxyethane (DME) or dioxane, the stereoisomer *trans*-**6** is obtained as the major compound, whereas in diethyl ether (Et_2O) or hexane, solvents with lower $E_T(30)$ values, the stereoisomer *cis*-**6** was the main product (Table 1). It is worth to mention that, to the best of our knowledge, studies correlating solvent properties and stereoselectivity of this kind of reaction are not very common in the literature.

On the basis of the data gathered in Table 1, it can be deduced that the selectivity in this reaction seems to be controlled mainly by the solvent, since the change of temperature is not very significant in general. In fact, the most important effect was observed when the reaction was refluxed in dioxane, the solvent with the highest boiling point (Table 1, entries 7 and 8). The best selectivity in favour of *cis*-**6** was achieved with Et_2O as solvent, at 30 and −78 °C,[9] however, the conversion at the latter temperature is slightly lower (Table 1, entries 9 and 11). Regarding *trans*-**6**, the best results concerning selectivity were observed in DME at 30 °C (Table 1, entry 5). Nonetheless, there was just a 50% conversion. When the reaction was conducted in the same solvent at 85 °C, the conversion reached 100% (Table 1, entry 6). Unfortunately, the selectivity decreased slightly and a more complex mixture of products was observed. The best option for the synthesis of *trans*-**6** considering both, conversion and selectivity, is to carry out the reaction in THF at 0 °C (Table 1, entry 2). In these conditions, this isomer was obtained in a good overall yield after column chromatography.

As previously mentioned, similar results to those obtained in THF, DME or dioxane have been reported in the literature for other ketones.[8d–f] As expected, when these solvents were used, *trans*-**6** was the major product[9] (Table 1). This result can also be explained if the organomagnesium compound attacks following the mechanism of the Felkin–Ahn model,[10] in which, the bulky substituent is located almost orthogonal to the carbonyl group, allowing the nucleophile to attack *anti* to this substituent and avoid steric repulsions. A graphic representation is shown in Figure 2.

In contrast, the use of Et_2O or hexane led to the other stereoisomer, *cis*-**6**, as the major product.[9] This change of selectivity can also be understood taking into account the different behaviour of the organomagnesium compound in solvents like Et_2O or hexane that might favour formation of the chelating intermediate represented in Figure 2. In this case, the addition probably follows the chelation model,[8] where the nucleophilic attack takes place from the opposite face, and therefore the other isomer is obtained.

Compounds *cis*-**6** and *trans*-**6** were isolated after column chromatography and their stereochemistry was assigned by 2D NOESY experiments. These experiments were performed using phase-sensitive ge-2D NOESY[11] in $CDCl_3$ and showed, as main facts, positive cross-peaks between the N*H*Ac and CH_3 signals for compound *trans*-**6**, and between CH_2OTBDPS and CH_3 for compound *cis*-**6**. The absence of cross-peaks between the N*H*Ac and CH_3 signals confirms the relative configuration of the latter one (Fig. 3).

After isolation of *cis*-**6** and *trans*-**6**, simple transformations of the functional groups are required to achieve the c_4-threoninols. All the protected groups in both the compounds were removed by hydrolysis in a 3 N HCl aqueous solution at 70 °C, to give the hydrochloride salts of *cis*-**1** and *trans*-**1**, respectively, in good yields (Scheme 3).

c_4-Threoninols with different protection patterns are necessary for synthetic purposes. In this context, the orthogonal protection of derivatives **6** was achieved by introduction of the methoxymethyl (MOM) group in the secondary alcohol. Thus, treatment of *cis*-**6** and *trans*-**6** with methoxymethyl chloride (MOMCl) and diisopropylethylamine (DIEA) led to *cis*-**7** and *trans*-**7**, respectively, in good overall yields (Scheme 4).

To obtain derivatives with the two alcohol groups free, the primary alcohol functions of *cis*-**6** and *trans*-**6** (protected with TBDPS) were reacted with tetrabutyl ammonium fluoride (TBAF) in THF at room temperature. In this way *cis*-**8** and *trans*-**8** were cleanly obtained (Scheme 4).

Table 1
Conditions and results for the addition of MeMgBr to cyclobutanone **5** as depicted in Scheme 2

Entry	Solvent	T (°C)	Conversion[a]	Yield %[b]	*cis*-**6**/*trans*-**6** ratio[c]
1	THF	−78	25		24/76
2	THF	0	100	77	19/81
3	THF	30	100	80	22/78
4	THF	66	100		26/74
5	DME	30	50		10/90
6	DME	85	100	52[d]	18/82
7	Dioxane	30	60		31/69
8	Dioxane	101	100	41[d]	50/50
9	Et_2O	−78	90		70/30
10	Et_2O	0	100	86	62/38
11	Et_2O	30	100	90	70/30
12	Hexane	30	75		61/39
13	Hexane	69	75		57/43

[a] Determined by ^{1}H NMR and/or HPLC.
[b] Yield after column chromatography.
[c] See Ref. 9.
[d] At these high temperatures, the yield decreased due to the formation of several unidentified sideproducts.

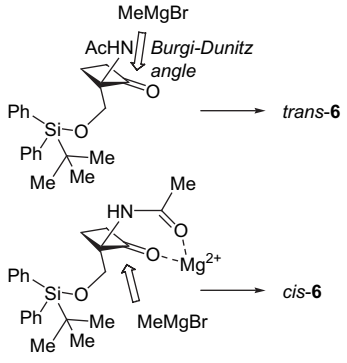


Figure 2. Felkin–Ahn (up) and chelation (bottom) models.

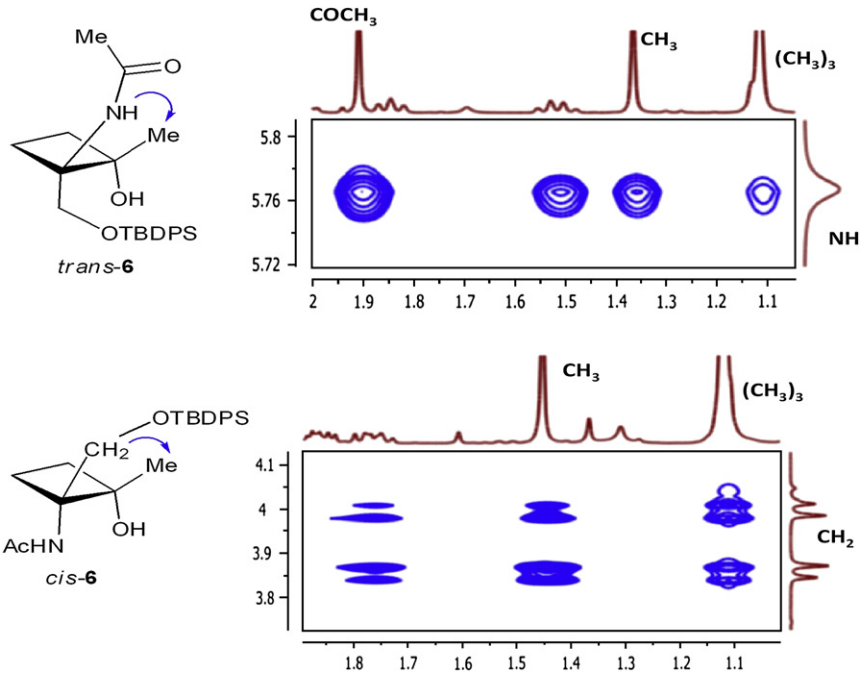
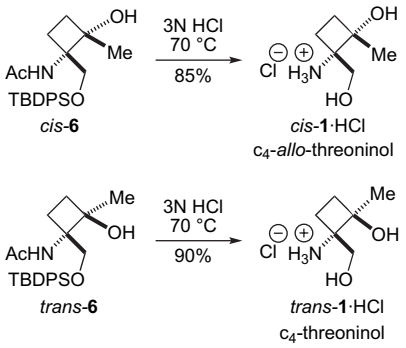
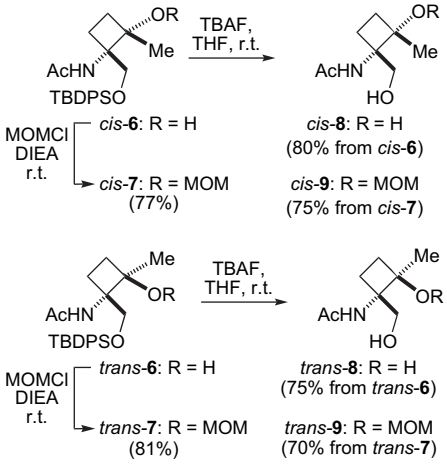


Figure 3. 2D-NOESY experiments of *trans*-**6** (up) and *cis*-**6** (bottom).



Scheme 3. Synthesis of c_4-threoninols *cis*-**1** and *trans*-**1**.



Scheme 4. Synthesis of differently protected c_4-threoninols.

Finally, to synthesize the primary alcohol protected c_4-threoninols *cis*-**9** and *trans*-**9**, their corresponding *cis*-**7** and *trans*-**7** precursors were subjected to the silyl group cleavage using again TBAF in THF (Scheme 4).

3. Conclusions

In summary, we have developed a synthesis of new 2-amino-1,3-diols with cyclobutane structure in different protected and unprotected forms, to be used in the synthesis of other interesting compounds. The key step, which can be modulated by the solvent, was the addition of methylmagnesium bromide to the corresponding cyclobutanone derivative, allowing to obtain the required products in good overall yields and selectivities.

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer using $CDCl_3$ with TMS as the internal standard or using CD_3OD or D_2O with TMS as the external standard with a coaxial microtube (chemical shifts are reported in parts per million on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^1H NMR spectra was made on the basis of coupling constants, ge-COSY experiments and ge-HSQC experiments on a Bruker AVANCE 400 spectrometer. This spectrometer was also used for 2D NOESY experiments described in the text. These experiments were processed with Mestre Nova software (Mestrelab Research, Spain). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

*4.1.1. trans-N-(2-Hydroxy-1-(tert-butyldiphenylsilyloxymethyl)-2-methylcyclobutyl)acetamide (trans-**6**)*

Compound **5** (1 g, 2.5 mmol) was solved in dry THF (50 mL) and was cooled to 0 °C. Then, 2.5 mL of MeMgBr (3 M in THF) was slowly added. The resulting solution was stirred for 14 h at this

temperature. A saturated NH_4Cl solution was added (20 mL) and the aqueous phase was washed with ethyl acetate (3×30 mL). The organic phase was dried, filtered, and concentrated in vacuo to give a mixture of compounds *cis*-**6** and *trans*-**6** in an 81:19 ratio in favour of compound *trans*-**6**. The mixture was separated by column chromatography (hexane/ethyl acetate, 1:1) to give 625 mg of compound *trans*-**6** and 175 mg of compound *cis*-**6**, both as white solids (800 mg, 77%). Compound *trans*-**6**. Mp: 138–140 °C. ^{1}H NMR (CD_3OD) δ 1.07 (s, 9H, $C(CH_3)_3$), 1.32 (s, 3H, CH_3), 1.43–1.51 (m, 1H, H_3), 1.78–1.83 (m, 1H, H_4), 1.87 (s, 3H, $COCH_3$), 1.94–2.03 (m, 1H, H_4), 2.10–2.16 (m, 1H, H_3), 3.06 (s, 1H, OH), 3.98 (d, 1H, J=10.8, CH_2O), 4.25 (dd, 1H, J=2.0, J=10.8, CH_2O), 5.73 (br s, 1H, NH), 7.36–7.43 (m, 6H, Ph), 7.60–7.65 (m, 4H, Ph). ^{13}C NMR (CD_3OD) δ 19.4 ($C(CH_3)_3$), 22.1 (C_4), 23.0 (CH_3CO), 24.2 (CH_3), 27.0 ($C(CH_3)_3$), 30.7 (C_3), 63.4 (CH_2O), 64.0 (C_1), 74.7 (C_2), 127.7, 129.7, 133.5, 135.5 (Ph), 170.3 (CO). ESI^+ (m/z)=412.7. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.15; H, 8.10; N, 3.45.

4.1.2. *cis-N-(2-Hydroxy-1-(tert-butyldiphenylsilyloxymethyl)-2-methylcyclobutyl)acetamide (cis-**6**)*

Compound **5** (1 g, 2.5 mmol) was solved in dry Et_2O (50 mL) at 30 °C. Then, 2.5 mL of MeMgBr (3 M in Et_2O) was slowly added. The resulting solution was stirred for 14 h at this temperature. A saturated NH_4Cl solution was added (20 mL) and the aqueous phase was washed with ethyl acetate (3×30 mL). The organic phase was dried, filtered and concentrated in vacuo to give a mixture of compounds *cis*-**6** and *trans*-**6** in a 70:30 ratio in favour of compound *cis*-**6**. The mixture was subjected to column chromatography (hexane/ethyl acetate, 1:1) to give 656 mg of compound *cis*-**6** and 282 mg of compound *trans*-**6**, both as white solids (938 mg, 90%). Compound *cis*-**6**. Mp: 144–146 °C. ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 1.40 (s, 3H, CH_3), 1.67–1.75 (m, 1H, H_4), 1.79–1.87 (m, 1H, H_3), 1.94 (s, 3H, $COCH_3$), 2.05–2.12 (m, 1H, H_3), 2.25–2.32 (m, 1H, H_4), 2.98 (br s, 1H, OH), 3.81 (d, 1H, J=10.4, CH_2O), 3.94 (d, 1H, J=10.4, CH_2O), 6.22 (br s, 1H, NH), 7.37–7.43 (m, 6H, Ph), 7.61–7.64 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$) δ 19.3 ($C(CH_3)_3$), 23.1 (C_4), 23.7 (CH_3CO), 23.9 (CH_3), 26.9 ($C(CH_3)_3$), 32.1 (C_3), 64.1 (C_1), 64.8 (CH_2O), 76.1 (C_2), 127.8, 129.9, 133.2, 135.5 (Ph), 171.1 (CO). ESI^+ (m/z)=412.7. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.10; H, 8.12; N, 3.38.

4.1.3. *trans-2-Amino-2-(hydroxymethyl)-1-methylcyclobutanol hydrochloride salt (trans-**1**·HCl)*

The white solid *trans*-**6** (50 mg, 0.12 mmol) was suspended in an aqueous 3 N HCl solution (10 mL) and the mixture was heated at 70 °C. After stirring for 4 h, the solvent was evaporated in vacuo and the resulting residue was partitioned between H_2O and ethyl acetate. The aqueous phase was concentrated in vacuo to give the product *trans*-**1**·HCl (c_4-threoninol) as a pale oil (18 mg, 90%). ESI^- (m/z)=132.3. ^{1}H NMR (D_2O) δ 1.44 (s, 3H, CH_3), 2.07–2.13 (m, 4H, CH_2), 3.80–3.92 (m, 2H, CH_2OH). ^{13}C NMR (D_2O) δ 24.6, 24.8, 33.4, 64.2, 66.1, 76.4. Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 43.01; H, 8.40; N, 8.29.

4.1.4. *cis-2-Amino-2-(hydroxymethyl)-1-methylcyclobutanol hydrochloride salt (cis-**1**·HCl)*

The white solid *cis*-**6** (50 mg, 0.12 mmol) was suspended in an aqueous 3 N HCl solution (10 mL) and the mixture was heated at 70 °C. After stirring for 3 h, the solvent was evaporated in vacuo and the resulting residue was partitioned between H_2O and ethyl acetate. The aqueous phase was concentrated in vacuo to give the product *cis*-**1**·HCl (c_4-*allo*-threoninol) as a pale oil (17 mg, 85%). ESI^- (m/z)=132.3. ^{1}H NMR (D_2O) δ 1.48 (s, 3H, CH_3), 1.73–1.89 (m, 1H, CH_2), 1.95–2.07 (m, 3H, CH_2), 3.92 (q, J=6.9, 2H, CH_2OH). ^{13}C NMR (D_2O) δ 21.5, 22.8, 31.6, 62.2, 64.1, 74.5. Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.98; H, 8.38; N, 8.31.

4.1.5. *trans-N-(2-Methoxymethyloxy-1-(tert-butyldiphenylsilyloxymethyl)-2-methylcyclobutyl)acetamide (trans-**7**)*

Compound *trans*-**6** (200 mg, 0.49 mmol) was solved in DIEA (1.0 mL, 5.8 mmol), under argon atmosphere, at 0 °C. After that, MOMCl was added (0.37 mL, 4.86 mmol) and the mixture was maintained at this temperature for 1 h. The temperature was then increased to room temperature and the reaction was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with H_2O (2×20 mL) and brine (2×10 mL). The organic layer was dried, concentrated in vacuo and purified by silica gel column chromatography (hexane/ethyl acetate, 1:1) to give the product *trans*-**7** (180 mg, 81%) as a colourless oil. ESI^+ (m/z)=456.7. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, $C(CH_3)_3$), 1.40 (s, 3H, CH_3), 1.80–1.85 (m, 2H, H_3, H_4), 1.92 (s, 3H, $COCH_3$), 1.96–2.12 (m, 2H, H_3, H_4), 3.25 (s, 3H, OCH_3), 3.88 (d, 1H, J=10.6, CH_2OSi), 4.33 (d, 1H, J=10.6, CH_2OSi), 4.54 (d, 1H, J=7.1, CH_2OCH_3), 4.78 (d, 1H, J=7.1, CH_2OCH_3), 5.55 (br s, 1H, NH), 7.36–7.44 (m, 6H, Ph), 7.65–7.67 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$) δ 19.5 ($C(CH_3)_3$), 20.8 (CH_3), 22.6 (C_4), 23.9 ($COCH_3$), 27.0 ($C(CH_3)_3$), 30.0 (C_3), 55.3 (OCH_3), 63.2 (CH_2OSi), 64.6 (C_1), 80.4 (C_2), 92.2 (CH_2OCH_3), 127.7, 127.8, 129.7, 133.7, 133.8, 135.7 (Ph), 169.4 (CO). Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.56; H, 8.14; N, 3.03.

4.1.6. *cis-N-(2-Methoxymethyloxy-1-(tert-butyldiphenylsilyloxymethyl)-2-methylcyclobutyl)acetamide (cis-**7**)*

Compound *cis*-**6** (260 mg, 0.63 mmol) was solved in DIEA (1.3 mL, 7.6 mmol), under argon atmosphere, at 0 °C. Then, MOMCl was added (0.48 mL, 6.3 mmol) and the mixture was maintained at this temperature for 1 h. The temperature was then increased to room temperature and the reaction was stirred for 14 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with H_2O (2×20 mL) and brine (2×10 mL). The organic phase was dried and concentrated in vacuo and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 7:3) to give product *cis*-**7** (220 mg, 77%) as a colourless oil. ESI^+ (m/z)=456.7. ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 1.50–1.57 (m, 4H, CH_3, H_4), 1.78 (t, 1H, J=8.7, H_3), 1.94 (s, 3H, $COCH_3$), 2.18–2.26 (m, 2H, H_3, H_4), 3.45 (s, 3H, OCH_3), 3.62 (d, 1H, J=10.8, CH_2OSi), 4.18 (d, 1H, J=10.8, CH_2OSi), 4.78 (d, 1H, J=6.7, CH_2OCH_3), 4.83 (d, 1H, J=6.7, CH_2OCH_3), 6.72 (br s, 1H, NH), 7.36–7.42 (m, 6H, Ph), 7.62–7.66 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$) δ 19.3 ($C(CH_3)_3$), 20.5 (CH_3), 20.8 (C_4), 24.1 ($COCH_3$), 26.9 ($C(CH_3)_3$), 31.0 (C_3), 55.6 (OCH_3), 63.1 (CH_2OSi), 64.0 (C_1), 78.7 (C_2), 92.0 (CH_2OCH_3), 127.5, 127.6, 129.6, 133.4, 133.6, 135.6 (Ph), 169.3 (CO). Anal. Calcd for $C_{26}H_{37}NO_4Si$: C, 68.53; H, 8.18; N, 3.07. Found: C, 68.52; H, 8.17; N, 3.02.

4.1.7. *trans-N-(2-Hydroxy-1-(hydroxymethyl)-2-methylcyclobutyl)acetamide (trans-**8**)*

To a solution of *trans*-**6** (390 mg, 0.95 mmol) in dry THF (20 mL), TBAF (0.95 mL, 1 M in THF) was added and the mixture was stirred for 1 h at room temperature. Then, the reaction was concentrated in vacuo and the residue was purified by silica gel column chromatography (MeOH/ethyl acetate, 5:95) to obtain the product *trans*-**8** as a white solid (120 mg, 75%). Mp: 130–132 °C. ^{1}H NMR (CD_3OD) δ 1.28 (s, 3H, CH_3), 1.54–1.57 (m, 1H, H_4), 1.77 (t, 1H, J=9.2, H_3), 1.91–1.95 (m, 5H, $COCH_3$, H_3, H_4), 3.75 (d, 1H, J=11.6, CH_2O), 4.13 (d, 1H, J=11.6, CH_2O). ^{13}C NMR (CD_3OD) δ 22.8, 22.8 ($COCH_3$, C_4), 24.2 (CH_3), 32.3 (C_3), 63.1 (CH_2O), 65.3 (C_1), 76.6 (C_2), 173.3 (CO). ESI^+ (m/z)=174.3. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.49; H, 8.75; N, 8.07.

4.1.8. *cis*-N-(2-Hydroxy-1-(hydroxymethyl)-2-methylcyclobutyl)acetamide (*cis*-**8**)

To a solution of *cis*-**6** (90 mg, 0.22 mmol) in dry THF (8 mL), TBAF (0.22 mL, 1 M in THF) was added and the mixture was stirred for 3 h at 0 °C. Then, the reaction was evaporated in vacuo and the residue was purified by silica gel column chromatography (MeOH/ethyl acetate, 5:95) to obtain the product *cis*-**8** as a colourless oil (30 mg, 80%). ESI^+ (m/z)=174.3. ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H, CH_3), 1.84–1.88 (m, 2H, H_3, H_4), 2.00–2.07 (m, 5H, $COCH_3$, H_3, H_4), 3.67 (d, 1H, J=11.2, CH_2O), 3.86 (d, 1H, J=11.2, CH_2O), 6.93 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 23.4, 23.4 (CH_3, C_4), 23.8 ($COCH_3$), 32.2 (C_3), 64.2 (C_1), 64.7 (CH_2O), 74.6 (C_2), 172.2 (CO). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.44; H, 8.72; N, 8.11.

4.1.9. *trans*-N-(1-(Hydroxymethyl)-2-(methoxymethoxy)-2-methylcyclobutyl)acetamide (*trans*-**9**)

To a solution of *trans*-**7** (160 mg, 0.35 mmol) in dry THF (15 mL), TBAF (0.35 mL, 1 M in THF) was added and the mixture was stirred for 3 h at 0 °C. Then, the solution was diluted with ethyl acetate (15 mL) and washed with a saturated NH_4Cl solution (20 mL). The organic layer was dried, concentrated in vacuo, and purified by silica gel column chromatography (MeOH/ethyl acetate, 1:9), to give the compound *trans*-**9** as a colourless oil (50 mg, 70%). ESI^+ (m/z)=218.4. ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.83–1.93 (m, 2H, H_3, H_4), 1.96 (s, 3H, $COCH_3$), 2.09 (dd, 1H, J=10.1, J=20.2, H_3), 2.19 (dd, 1H, J=10.1, J=20.3, H_4), 3.34 (s, 3H, OCH_3), 3.76 (d, 1H, J=11.7, CH_2OH), 4.07 (d, 1H, J=11.7, CH_2OH), 4.62 (d, 1H, J=6.9, CH_2OCH_3), 4.67 (d, 1H, J=6.9, CH_2OCH_3), 6.18 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 22.2 (C_4), 23.9 ($COCH_3$), 29.8 (C_3), 55.6 (OCH_3), 63.6 (C_1), 65.5 (CH_2OH), 81.4 (C_2), 91.8 (CH_2OCH_3), 170.5 (CO). Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.32; H, 8.75; N, 6.53.

4.1.10. *cis*-N-(1-(Hydroxymethyl)-2-(methoxymethoxy)-2-methylcyclobutyl)acetamide (*cis*-**9**)

To a solution of *cis*-**7** (220 mg, 0.48 mmol) in dry THF (20 mL), TBAF (0.48 mL, 1 M in THF) was added and the mixture was stirred for 3 h at 0 °C. Then, the solution was diluted with ethyl acetate (20 mL) and washed with a saturated solution of NH_4Cl (20 mL). The organic layer was dried, concentrated in vacuo, and purified by silica gel column chromatography (MeOH/ethyl acetate, 1:9), to give the compound *cis*-**9** as a colourless oil (80 mg, 75%). ESI^+ (m/z)=218.4. ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H, CH_3), 1.77–1.90 (m, 2H, H_3, H_4), 2.03 (s, 3H, $COCH_3$), 2.08–2.21 (m, 2H, H_3, H_4), 3.39 (s, 3H, OCH_3), 3.61 (d, 1H, J=11.6, CH_2OH), 3.88 (dd, 1H, J=6.5, J=11.6, CH_2OH), 4.27 (d, 1H, J=3.8, OH), 4.67 (d, 1H, J=6.9, CH_2OCH_3), 4.71 (d, 1H, J=6.9, CH_2OCH_3), 6.96 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_3), 22.7 (C_4), 24.0 ($COCH_3$), 30.5 (C_3), 55.8 (OCH_3), 64.5, 64.8 (C_1, CH_2OH), 79.1 (C_2), 92.1 (CH_2OCH_3), 171.5 (CO). Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.34; H, 8.84; N, 6.47.

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9. The cis/trans ratio was determined by ^1H NMR and HPLC when signal overlapping was observed in the ^1H NMR reaction crude spectra. Thus, the data in entries 2, 3 and 10 in Table 1 correspond to ^1H NMR experiments, whereas for the rest of the entries, both the analyses were carried out. HPLC sampling was performed at a flow rate of 1 mL/min (CH_3CN/H_2O, 60/40) using a Phenomenex® column, Luna 5 μm C18(2) 100A, 250×4.6 mm. Injection volume=20 μL. Detector λ=254 nm. Retention times for *cis*-**6** and *trans*-**6** are 19.6 and 20.4 min, respectively.
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