Highly Diastereoselective Methylation of Five-Ring *N*,*O*-Acetals

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Abstract: Highly diastereoselective methylation of (2*S*,4*S*)- and (2*R*,4*S*)-3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**1a**/**b**) is reported. The relative and absolute configuration of the methylated products was assigned by NOESY and confirmed by a crystal structure of **1a**.

Keywords: Amino acids, alkylation, diastereoselectivity.

INTRODUCTION

In the course of our studies towards new synthetic routes for sphingosine-related metabolites [1] such as myriocin [2], mycestericins [3], and sphingofungins [4], we became interested in α substituted amino acids [5] (Fig. **1**). We chose the principle of self-regeneration of stereocenters (SRS) [6] as the general synthetic strategy for these compounds. For these purposes, L-serine is a convenient starting material since it already contains all the functionalities of the hydrophilic end of the metabolites. For stereoselective α alkylation of this particular amino acid, a new stereogenic center is transiently introduced via formation of oxazolidines of type **1**. Although similar oxazolidines have previously been prepared, we herein report new alkylation products. In contrast to recent literature, we have not only regenerated configuration at the defined stereocenter, but we have also prepared a product of inversion [6,7].

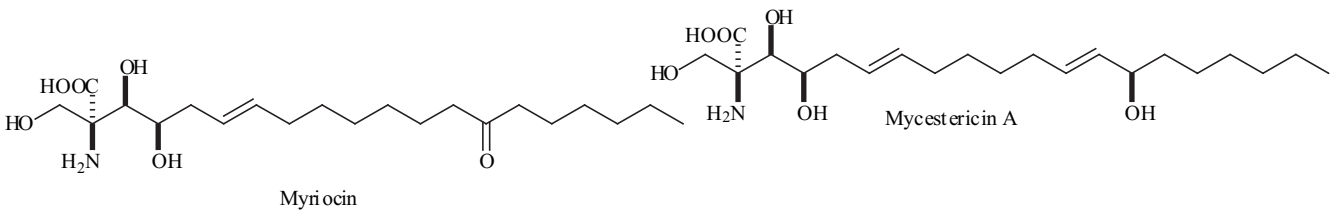

Fig. (1). Examples of Sphingosine-related Metabolites.

RESULTS AND DISCUSSION

The oxazolidines used in our alkylation studies were prepared according to standard methods (**1a**), or with a slightly modified literature procedure (**1b**) [7,8]. Compound **1a** [9] was isolated from a 3:1 mixture together with **1b** [10], while diastereopure **1b** was obtained in three steps from L-serine (Scheme **1**) [7]. Oxazolidines derived from serine esters are prone to ring-chain tautomerism [11]. Equilibrium studies of serine methyl and ethyl esters with aromatic aldehydes in $CDCl_3$ have shown three-component tautomeric mixtures where the open-chain Schiff base intermediate was typically predominating. Among the two ring forms the amount of the *cis* epimer was always higher than that of the *trans* epimer and, unlike the thiazolidines [12], no reaction conditions could be found to obtain predominantly the *trans* product [11]. We used the bulky *N*-protecting group Boc together with the large *t*Bu ring substituent to obtain **1** in configurations where one face was maximally shielded from subsequent nucleophilic alkylation. In fact, **1a** was in solution a 9:1 mixture of rotamers while only one rotameric form was observed for **1b** [13].

Subsequent methylation reactions of the ester enolates of **1a** and **1b** were performed under standard conditions (Scheme **1**) [14]. Using 110 mol-% of LDA was sufficient to deprotonate **1b** but not **1a**. However, the alkylation yields were only modest, mainly starting material being recovered, indicating slow enolization. Increasing the amount of base to 200 mol-% and prolonging the enolization time up to one hour improved the yield of the methylated products significantly. In contrast to literature, the use of DMPU as a co-solvent did not affect the outcome of the alkylations [7,15]. The methylated products **3a** (87%) and **3b** (92%) were obtained in high yield and purity [16]. Compounds **3a**/**b** are enantiomers, which was confirmed by their identical NMR spectra and opposite signs of optical rotation.

The relative and thus also absolute configurations of **1a**/**b** and **3a**/**b** were determined with NOESY experiments

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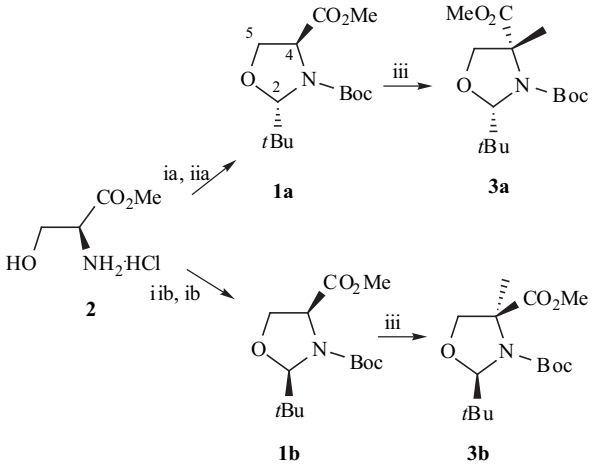
and confirmed by the crystal structure of **1a**. In the NOESY spectrum of **1b** (not shown) there is a clear correlation between the methyl protons of the *t*Bu and the acetal proton at C2 as well as the equatorial methylene proton at C5. The same correlations are observed for **3b**, too (Fig. **2**). Whereas there is no visible correlation between the pseudoaxial C5 proton and the C4 proton in **1b**, we observed a correlation of the pseudoaxial methylene proton at C5 with the C4-methyl protons in **3b**.

Based on the above arguments, the newly introduced substituent in **3b** is necessarily *trans* to the *t*Bu ring substituent. The relatively restricted rotational flexibility of **1a**/**b** is corroborated by broader resonance signals of the acetal proton at C2 and the *t*Bu/Boc methyl protons in the ^{1}H NMR spectra both in $CDCl_3$ and benzene-d_6 at room temperature.

An *ORTEP-3* [17] plot of **1a** confirms the NOESY observations and the *trans* configuration of the C2 and C4 ring substituents, and illustrates how one face of the molecule ring is shielded by the large ring substituents (Fig. **3**) [18].

In summary, selective formation of both diastereomers of 3-*tert*-butyl 4-methyl 2-*tert*-butyloxazolidine-3,4-dicarboxylate (**1a**/**b**) was achieved by two different routes, where the reversal of the order of protection steps is the main difference. Analytical data for **1a** and **1b** are presented for the first time and the observed structural and conformational properties were utilized to synthesise **3a** and **3b** in high purity, yield and *dr*. Further examples of this methodology and careful structural analysis of the highly substituted *N*,*O*-acetals will be reported in due course.



Scheme 1. Reagents and conditions: ia) $(Boc)_2O$, $MeOH/CH_2Cl_2$, r.t.; ib) $(Boc)_2O$, TEA/THF, r.t.; iia) toluene, reflux; iib) pivalaldehyde, TEA/pentane, reflux; iii) LDA, MeI, THF, -78 °C.

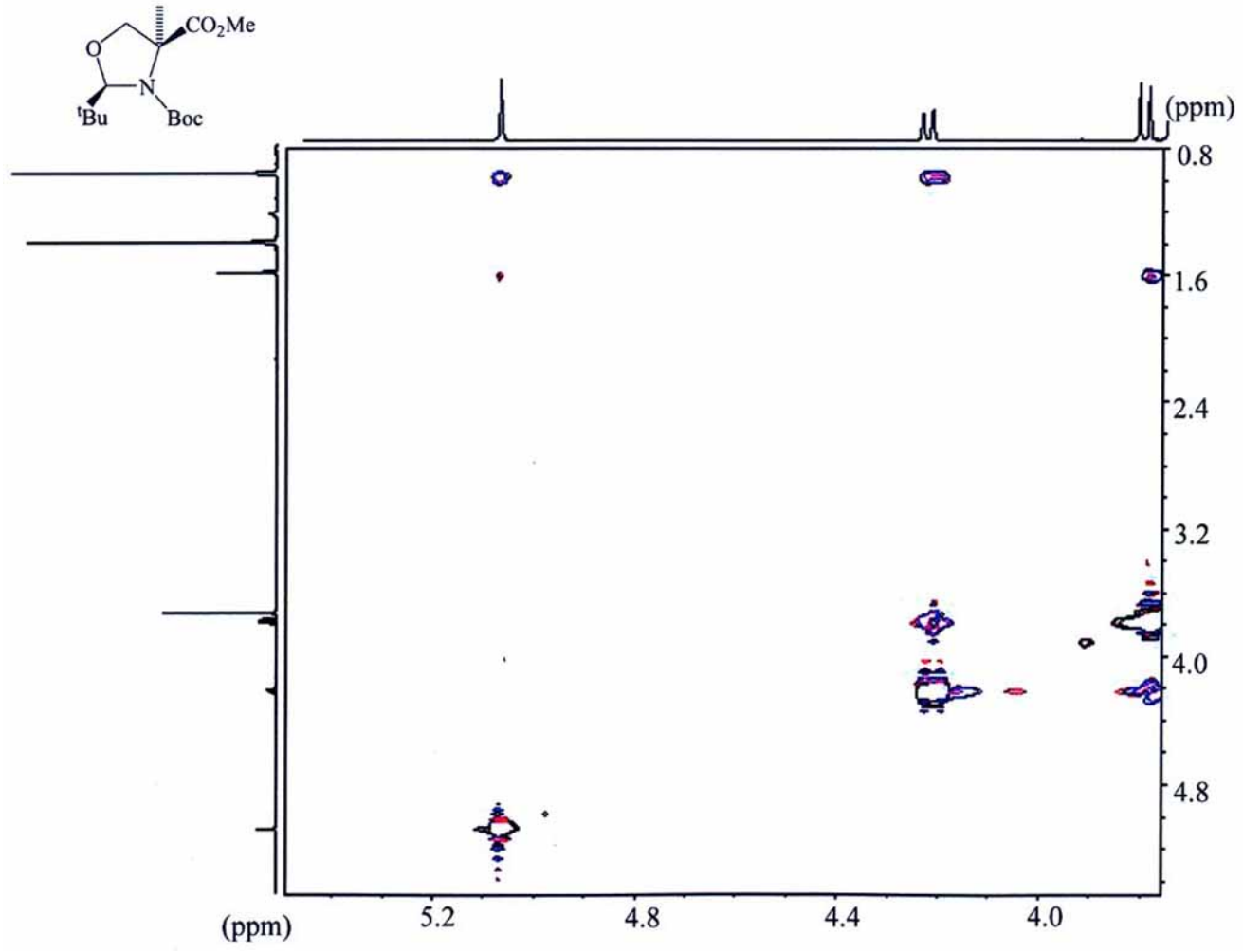


Fig. (2). NOESY spectrum of 3b.

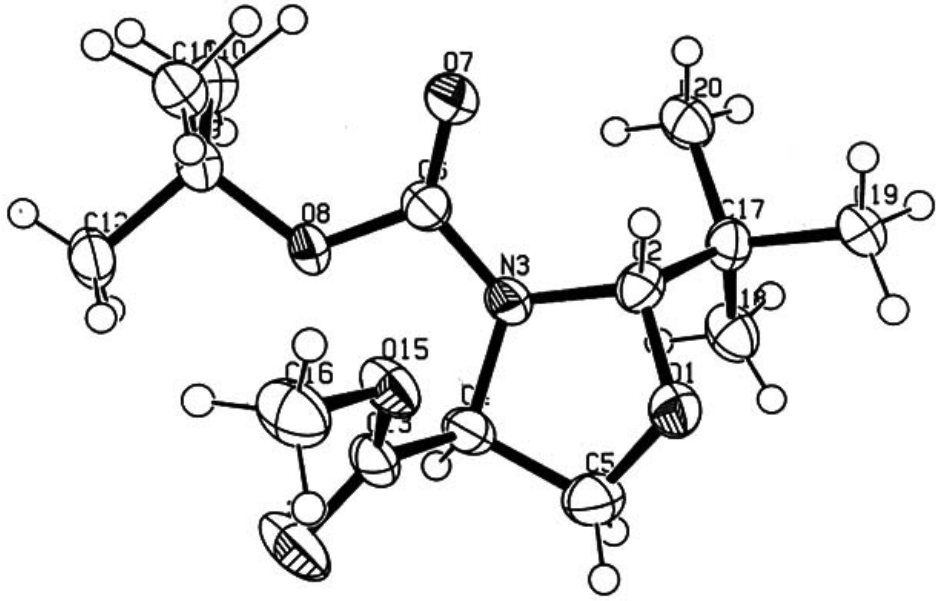


Fig. (3). *ORTEP-3* plot of **1a.**

ACKNOWLEDGEMENTS

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[9] **1a**: R_f = 0.17 (Hex/EtOAc 4:1). m.p. = 64-65 ºC (Hex). $[\alpha]^{20}_D$ = -57 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$), major rotamer, δ 5.17 (1H, br s), 4.33 (2H, m), 4.00 (1H, d, *J* = 7.2 Hz), 3.73 (3H, s), 1.43 (9H, br s), 0.93 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$), major rotamer, δ 172.0, 154.0, 96.8, 81.0, 70.4, 60.5, 52.3, 39.0, 28.1, 26.0. MS (EI) *m/z* 288 (M^+), 272, 232, 214, 200, 188, 174, 172, 160, 146 (BP), 130, 128, 112, 102, 86, 70, 57. Calcd. for $C_{14}H_{25}NO_5$: C, 58.46; H, 8.77; N, 4.88. Found C, 58.04; H, 8.72; N, 4.66.

[10] **1b**: R_f = 0.19 (Hex/EtOAc 4:1). $[\alpha]^{20}_D$ = -30 (*c* 0.3, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (1H, s), 4.67 (1H, br m), 4.24 (1H, dd, *J* = 5.6, 8.6 Hz), 4.11 (1H, t, *J* = 8.6 Hz), 3.73 (3H, s), 1.45 (9H, s), 0.91 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 155.1, 97.6, 81.3, 68.3, 59.7, 52.2, 37.7, 28.2, 25.8. HRMS calcd. for ($C_{14}H_{25}NO_5$ + H) 288.1810, found 288.1823.

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[13] Rotameric mixtures have been observed when the *N*-protection group was -CHO, see: ref. [7b].

[14] **General Procedure for Methylation:** A 50 ml flask was charged with THF (35 mL) and diisopropylamine (0.1 mL, 0.70 mmol). The solution was cooled to –78 °C and *n*-BuLi (0.70 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min, then **1** (0.35 mol) in THF (5 mL) was added at –78 °C. Methyl iodide (0.88 mmol) was added after stirring for 45 min at –78 °C. The reaction mixture was allowed to warm up to r.t. and then poured onto a mixture of semisaturated solution of NH_4Cl (30 mL) and Et_2O (80 mL). The organic layer was washed with dist. H_2O (4 × 50 mL) and dried over Mg_2SO_4.

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[16] **3a:** R_f = 0.16 (Hex/EtOAc 8:1). $[\alpha]^{20}_D$ = +4 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (1H, s), 4.25 (1H, d, *J* = 8.0 Hz), 3.80 (1H, d, *J* = 8.0 Hz), 3.75 (3H, s), 1.40 (9H, s), 1.00 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 154.1, 97.4, 81.2, 77.5, 66.8, 52.8, 39.6, 28.5, 26.9, 21.7. MS (EI) *m/z* 302 $(M+1)^+$, 296, 228, 214, 202, 186, 160 (BP), 114, 100, 84, 69, 58. HRMS calcd. for ($C_{15}H_{27}NO_5$ + H) 302.1967, found 302.1977. **3b**: $[\alpha]^{20}_D$ = -5 (*c* 0.4, $CHCl_3$).

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[18] Crystal data for **1a**: $C_{14}H_{25}NO_5$, M_r = 287.35, orthorhombic, space group $P2_12_12_1$, *a* = 5.9326(2), *b* = 10.1145(7), *c* = 26.3519(17) Å, α = 90°, β = 90°, γ = 90°, *U* = Å^3, *Z* = 4, *T* = 173(2) K, *F*(000) = 624, μ = 0.091 mm^{-1}, 10166 reflections measured of which 3627 were independent, full matrix least-square refinement on F^2, R_1 = 0.0931, wR_2 = 0.2306. Data collection, 10166 reflections, 3627 independent (R_{int} = 0.1295); Full matrix least squares refinement on F^2.