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Total diastereoselectivity in the one-pot multistep reaction of (R_S)-(+)-{[(4-methylphenyl)sulfinyl]methyl}-1-oxa-4-azaspiro[4.5]dec-3-ene and *E*-methyl cinnamate. An approach to (2*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-4,6-diphenyl-1-azabicycle[3.3.1]nonane

Carlos Alvarez-Ibarra [a,*], Juan F. Collados Luján [a], Maria L. Quiroga-Feijóo [a], Gonzalo Rodríguez [b]

[a] *Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, Ciudad Universitaria, s/n, 28040 Madrid, Spain*
[b] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 29049 Madrid, Spain*

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ABSTRACT

The base-mediated reaction of enantiomerically pure α-sulfinylketimine (+)-**1** with (*E*)-methyl cinnamate afforded (+)-**5a** in a one-pot procedure with complete diastereoselectivity. A sole diastereomer of the eight possible ones was isolated which revealed the stereocontrol of the chiral sulfinyl group in the construction of the three new stereogenic centres. The absolute configuration of stereocentres introduced in (+)-**5a** was assigned on the basis of ^{1}H NMR data and a single X-ray structure.

1. Introduction

We have reported several synthetic applications of compound **1** derived from *rac*-alaninol.[1] Among the most important ones, there is a method that leads to 4-alkyl/aryl-substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidine-2-ones **3** by reaction with alkyl ene-esters **2** in basic media. It implies the formation of an adduct via a Michael reaction followed by transenolization and cyclization of this intermediate in a one-pot procedure (Scheme 1).[2]

An important feature of this reaction is the diastereoselectivity in being able to reach 100% of the stereoisomer **3** if isopropyl esters are used. In addition it can be modulated in the reaction of **1** with methyl esters by changing the nature of the metallic ion in the reagent enolate.[2b] Compounds such as **3** are precursors of N-substituted 4-alkyl/aryl-2-piperidinylmethanols **4**, belonging to a new heterocyclic series of the chiral β-amino alcohols.[3] Our current research is focused on the synthesis and evaluation of these amino alcohols as chiral ligands in the catalytic dialkylzinc addition to aldehydes and ketones.[4]

In particular, we have attempted to synthesize conformationally restricted β-amino alcohols, such as **6**, which are stereoanalogues of compound **4**. With these goals in mind, and since the 1-azabycicle[3.3.1]nonane building block can be achieved from the glutaric amide-ester moiety of the compound **5**, we herein report the optimal conditions to obtain **5a** (R_1 = Ph; R_2 = Me) in a one-pot procedure starting from **1**. Furthermore, it is accomplished with an enantiomeric purity of >95:5, indicated from the spectroscopic data (NMR) of the crude reaction.[5] The single crystal X-ray analysis of **5a** allows its relative configuration to be established; the absolute configuration takes into account the stereochemical outcome of the reaction.

2. Results and discussion

Since the diastereoselectivity was so high (>95:5), it seems that the actual stereochemical substrate has to be the rigid intermediate **3a** (R_1 = Ph). In order to confirm this hypothesis, compound **3a** was isolated from the reaction of **1** with *E*-methyl cinnamate (1:1) using *n*-BuLi as a base (1:1) in a typical and well-established procedure,[6] yielding 61% of the (4*S*)-2-piperidone **3a**. The following reaction of **3a** with *E*-methyl cinnamate (1:2), under the same conditions that **3a** was achieved, gave **5a** with a high diastereoselectivity (>95:5) as determined by the analysis of the NMR spectroscopic data.[5] Compound **5a** was purified by chromatography on deactivated silica gel (hexane/ethyl acetate 4:1 v/v) to give white crystals (59% yield) {mp 163–166 °C; $[\alpha]_D$ = +188.4 (*c* 0.4, $CHCl_3$)}. Its relative configuration was established from the single crystal X-ray structure, which is shown in Figure 1.

The molecule has four stereogenic centres with the following absolute configurations: S1 (*S*), C9 (*S*), C10 (*R*) and C26 (*R*). The more significant angles around S1 are C8S1C1, 97.0(3); O1S1C8, 108.2(2), and O1S1C1, 106.5(2) near to the tetrahedrical geometry.

The atoms C8C9C11N1C12 in the cyclohexene ring are nearly planar [N1, 0.0027(5) and C11, −0.023(5) Å at the maximum deviation] with C10 deviating for −0.619(5) Å from the mean plane.

The oxazolidine ring exhibits an envelope conformation with O4 at −0.366(5) Å, whereas N1C12C13C14 are practically in a

* Corresponding author. Tel.: +34 91 394 4223; fax: +34 91 394 4103.
E-mail address: caibarra@quim.ucm.es (C. Alvarez-Ibarra).

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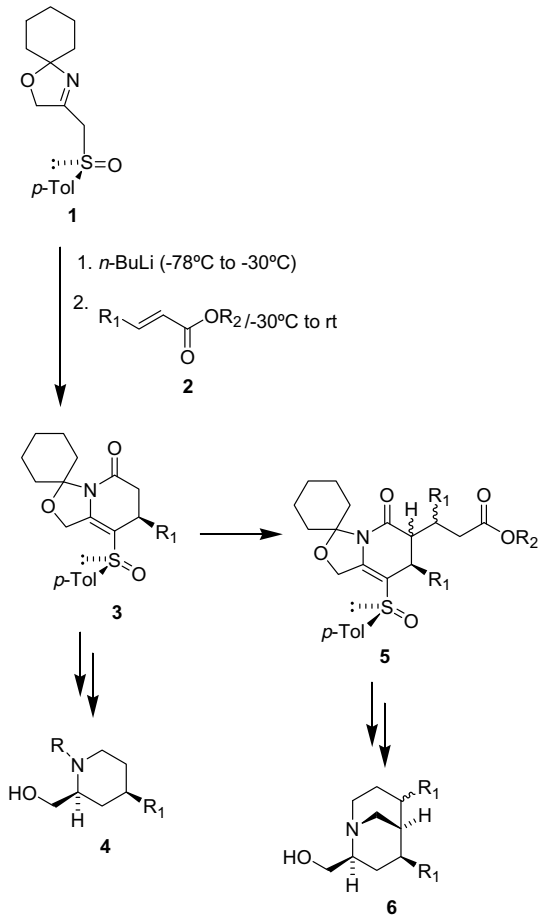

Scheme 1.

plane (N1, 0.018 in the maximum deviation). Moreover, a steric effect around the spiranic centre was observed for C15–C16, 1.561(7) Å and C14–N1, 1.493(5) Å. On the other side, atoms C15C16C18C19 are practically planar with C14 and C17 atoms deviating from the mean plane in 0.605(5) and −0.671(5) Å in a nearly chair conformation. The phenyl rings are planar within experimental error while the benzyl atoms C9 and C26 are practically in the same plane as their respective phenyl rings. It is interesting to note that the phenyl ring joined to the C9 atom is proximately parallel to that joined to the sulfinyl group but no intramolecular contacts are observed because the distance within the centroids reaches 3.515(5) Å.[7,8]

The structure of the 3,4-*syn* adduct **5a** is in accordance with a *Re*-facial diastereoselectivity of the lithium enolate **3a** (*anti* versus the phenyl group joined to the C9 atom), and a *Si*-facial one of the *E*-methyl cinnamate (Fig. 2). This approach appears to be favoured because it allows the complexation of the lithium ion by the O5 atom and the C27 carbanionic one in the transition state. Furthermore, it avoids the 1,3-quasi axial interactions involving the phenyl group of the ester to be developed as shown in Figure 2. It should be noted that an eight-membered cyclic transition state seems to be too flexible for effective transfer of the chirality of the enolate and in turn, a six-membered ring involving the lithium ion has been proposed.

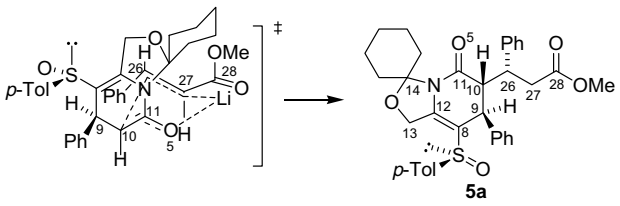

Figure 2. *Re*-Facial and simple diastereoselectivities in the reaction of Li^{+}-**3a** enolate and *E*-methyl cinnamate **2**.

In order to achieve the synthesis of **5a** in a one-pot procedure, the reaction was carried out by starting from **1** (0.5 mmol in 1.5 mL of THF), *n*-BuLi (1.1 mmol) and *E*-methyl cinnamate (1.2 mmol; 0.6 M solution in THF) following the general procedure described herein.[6] After the addition of the ene-ester, the reaction mixture was allowed to reach room temperature and was monitor-

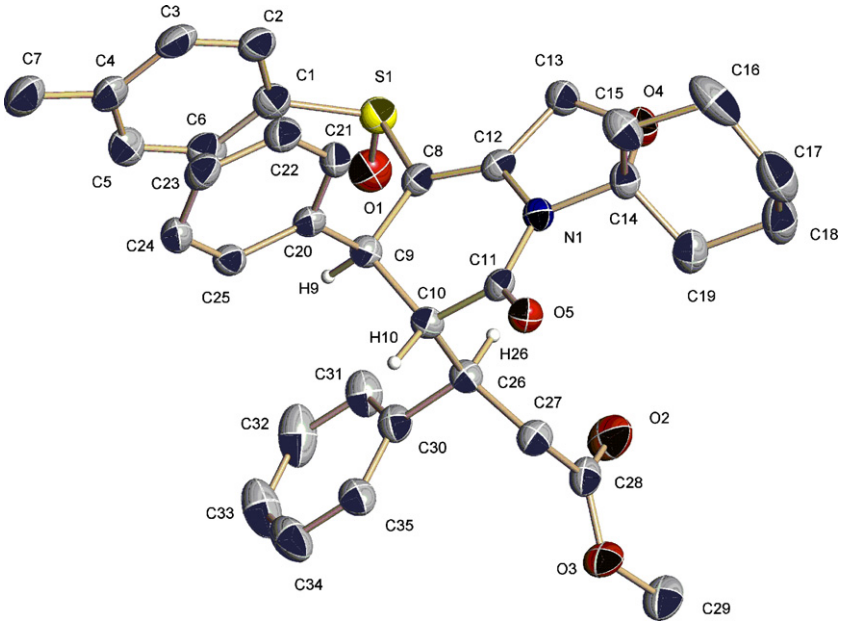

Figure 1. ORTEP drawing of (+)-**5a** showing the atom-numbering scheme. Atoms of hydrogen at non-chiral centres are omitted for the sake of simplicity.[8]

ized by TLC (silica gel; hexane/ethyl acetate 4:1, v/v). Thus, it was observed that the formation of **3a** was complete after 1 h while its disappearance, related to the appearance of compound **5a**, was complete after 2 h. The workup of the reaction mixture required the addition of methanol (0.1 mL) and, then, the evaporation of solvent to avoid hydrolysis of the ester product. The residue was diluted with ethyl acetate and then filtered through a pad of Celite; the filtrate was concentrated at reduced pressure at rt. The residue was purified by flash chromatography on deactivated silica gel (hexane/ethyl acetate: 4:1, v/v). The isolated product (244 mg, 0.4 mmol) was obtained as a white solid (83% yield; Mp 163–166 °C, $[\alpha]_D$ = +188.4 (c 0.4, $CHCl_3$)). Its structure was determined from the spectroscopic NMR data and it was identical to the previous ones recorded for the sole product accomplished from **3a** in the two-step procedure.

3. Conclusion

In conclusion, a key intermediate in the route to enantiomerically pure and conformationally restricted 2-piperidinyl methanols such as **6** has been accomplished from the chiral α-sulfinyl ketimine **1** and *E*-methyl cinnamate in a one-pot procedure using *n*-BuLi as a base (83% yield). We are currently exploring the chemistry of this multifunctional heterocycle to give **6a** (R_1 = Ph) as well as trying to extend the scope of this route to introduce different functionality in the adducts such as **5**.

Acknowledgements

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5. Compound **5a** [83% from (*S*)-(+)-**3**]. Mp 163–166 °C (from ethanol). $[\alpha]_D$ +188.4 (*c* 0.4, $CHCl_3$). IR ($CHCl_3$) ν_{max}/cm^{-1}: 1739.7, 1689.5, 1654.8. ^1H NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.60–6.30 (m, 14H, ArH), 5.25 (s, 2H, H13), 3.46 (s, 3H, OMe), 3.37 (s, 1H, H9), 3.30 (ddd, 1H, $J_{1,3}$ = 11.0, 9.2, 6.2 Hz, H26), 2.69 (subsystem AB, 1H, J_{AB} = 15.8, $J_{1,3}$ = 9.2 Hz, H27 or H27′), 2.67 (subsystem AB, 1H, J_{AB} = 15.8, $J_{1,3}$ = 6.2 Hz, H27′ or H27), 2.61 (d, 1H, *J* = 11.4 Hz, H10), 2.5–2.3 (m, 2H, cyclohexyl), 2.18 (s, 3H, Me (Tol)), 1.9–1.6 (m, 7H, cyclohexyl), 1.31 (m, 1H, cyclohexyl). ^{13}C NMR δ_C (125 MHz; $CDCl_3$; Me_4Si) 172.1 (C11), 167.1 (C28), 143.6, 141.6, 140.7, 140.5, 138.0 (C1, C4,C12, C20, C30), 129.6, 129.1, 129.0, 128.8, 127.8, 126.8, 126.5, 125.1 (C–H Ar), 112.7 (C8), 99.7 (C14), 65.4 (C13), 58.2 (C10), 51.9 (C29), 42.3 (C26), 39.6 (C9), 39.5 (C27), 33.7, 32.3, 24.8, 23.3, 23.2 (cyclohexyl), 21.6 (Me-Tol). Anal. Calcd for $C_{35}H_{37}NO_5S$: C, 72.01; H, 6.39; N, 2.40. Found: C, 72.17; H, 6.22; N, 2.51.
6. *General procedure*: To a cold (−78 °C) solution of sulfinyl ketimine **1** (0.9 mmol) in dry THF (5 mL), was added a solution of *n*-BuLi (1.6 M in hexane, 0.67 mL, 1.07 mmol). The solution was stirred at −78 °C for 0.5 h, after which the temperature was raised to −30 °C and the *E*-ene ester **2** (1.2 mmol, 0.6 M solution in THF) was added. The reaction mixture was warmed to rt and was stirred for 2 h. The mixture was diluted with saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated at reduced pressure and chromatographied on deactivated silica gel to isolate 230 mg of **3a** as a pure diastereomer (61% yield). Compound **3a** was identified by its $[\alpha]_D$ = +29.7 (*c* 0.2, $CHCl_3$) and its NMR spectroscopic data in accordance with that reported.[2b]
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8. The crystallographic data for compound **5a** have been deposited in the Cambridge Crystallographic Data Centre No. CCDC 237968.