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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of a methylene group by asymmetric reduction of 2-methoxy-4,5-diphenyl-3-tosyl-1,3-oxazolidine

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Abstract

The synthesis of a homochiral methyl group (CHDT-), meaning that all three isotopes of hydrogen are present in a stereodefined fashion at the same carbon atom, requires the preparation of a homochiral methylene (-CHD-) group. Substitution of the exocyclic methoxy group of a diastereomeric mixture of 2-methoxy-4,5-diphenyl-3-tosyl-1,3-oxazolidine using a combination of metallic hydrides and Lewis acids allowed us to obtain a stereochemically defined methylene group.

1. Introduction

Since the pioneering work of Cornforth[1] and Arigoni,[2] chiral methyl groups, meaning that all three isotopes of hydrogen are present in a stereodefined fashion at the same carbon atom, have remained interesting challenges for synthetic chemists. This strong interest is not only due to the unique aspect of the 'smallest asymmetric' object ever synthesized,[3] but also because a chiral methyl group allows the elucidation of many chemical or biochemical reactions in which generation, conversion and transfer of methyl groups are crucial.[4] Many routes to the chiral methyl group have been published and generally involve the synthesis of a chiral methylene group. The presence of a 'masked' leaving group linked to this methylene group is also required to introduce the third isotope of hydrogen, and so a methylene group adjacent to an oxygen or a nitrogen atom is the most frequently designed synthon. Hitherto, the main methods of obtaining these chiral groups have involved asymmetric reduction of CO[5] or CN[6] double bonds. Very few reports have also demonstrated the viability of reductions of chiral aminals[7] or acetals or orthoesters,[8] in which the hydrogen label is introduced by means of labelled reducing agents.

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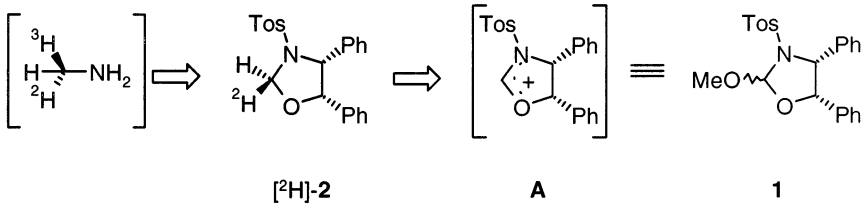
The main drawbacks of these approaches are the long synthetic routes and the numerous radiochemical steps:[9] a shorter approach is therefore desirable. We report here the first part of this project, the preparation of a formal enantiopure methylene group.

2. Results and discussion

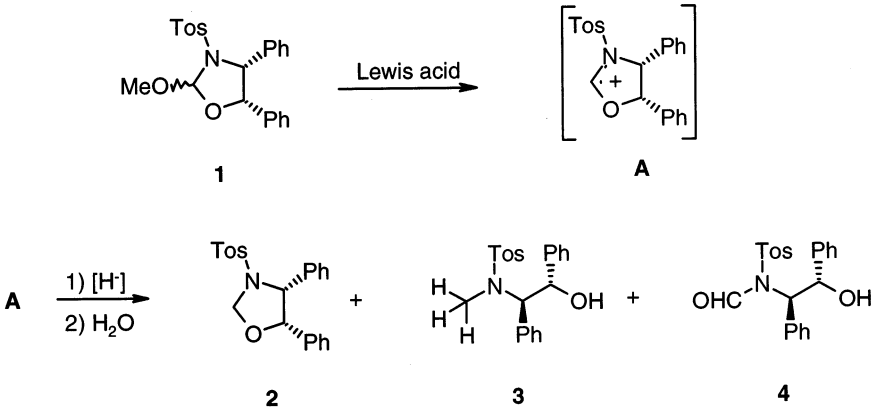
Our strategic route to chiral methylamine is exemplified by the following retrosynthetic pathway (Scheme 1):[10]



Scheme 1.

The key step of this route is based on the use of orthoamide **1** as a chiral formyl cation equivalent. We assumed that the postulated cationic intermediate **A** obtained from reaction of **1** with a suitable Lewis acid could be stereoselectively reduced by a hydride species to afford **2**. Our choice was made in connection with previous reports that clearly showed that the substitution of the exocyclic alkoxy group is usually achieved by various nucleophiles in a fairly good stereoselective fashion.[11] After a few preliminary experiments, we turned our attention to the (4*R*,5*S*)-2-methoxy-4,5-diphenyl-3-tosyl-1,3-oxazolidine. To our knowledge, no report has yet been published on the reduction of these 2-alkoxy-oxazolidines.

Compound **1** was easily obtained as a mixture of epimeric C2 (d.r. = 50/50) via an acid-catalyzed condensation of trimethyl orthoformate with (1*S*,2*R*)-*N*-Tos-diphenyl ethanolamine following a standard literature procedure.[12] When compound **1** is treated with a metallic hydride in the presence of a slight excess of Lewis acid, a mixture of three components is obtained, probably via the reaction of the postulated intermediate **A** (Scheme 2).



Scheme 2.

We first tried to find the best experimental conditions (Lewis acid, reductant, temperature, etc.) in order to obtain compound **2** as the major component. The results are summarized in Table 1. A combination of $Et_3SiH/BF_3{\cdot}OEt_2$ at low temperature and quenching at the same temperature proved to be unsatisfactory and we only observed product **4**, probably resulting from attack of water on intermediate **A** during the hydrolysis of the reaction mixture (entry 1). Since at low temperature the combination of these two reagents reacted sluggishly, we allowed the reaction mixture to warm to room temperature before hydrolysis, but in this case the major product was compound **3** resulting from the over-reduction of **2** (entry 2). This was even worse with a stronger Lewis acid such as $TiCl_4$ since only **3** was obtained, along with many degradation products (entry 3). Moving to borohydrides gave us satisfactory results since the use of $NaBH_4$ or $NaBH_3CN$ gave compound **2** as the major product in 43 and 61% yield, respectively (entries 4 and 5). Using n-Bu_4NBH_4 allowed us to obtain **2** as a single product in a fairly good yield (entry 6). Lastly, the best conditions that we have found so far were the combination of Bu_3SnH and $BF_3{\cdot}OEt_2$, and in this case only compound **2** was obtained in a good yield (82%, entry 7).

Table 1
Preparation of **2** from **1**

Entry	Hydride	Lewis acid	Time (h)	T (°C)	**2**/**3**/**4**	Yield[a]
1	Et_3SiH	$BF_3{\cdot}OEt_2$	4	−80	0/0/100	73[b]
2	Et_3SiH	$BF_3{\cdot}OEt_2$	20	−60→25	30/70/0	22
3	Et_3SiH	$TiCl_4$	4	−80→−50	0/100/0	25[c]
4	$NaBH_4$	$BF_3{\cdot}OEt_2$	6	−80→−20	51/0/49	43
5	$NaBH_3CN$	$BF_3{\cdot}OEt_2$	20	−80→25	70/15/15	61
6	Bu_4NBH_4	$BF_3{\cdot}OEt_2$	4	−80→−50	100/0/0	80
7	Bu_3SnH	$BF_3{\cdot}OEt_2$	4	−80→−50	100/0/0	82

[a] All reactions performed in CH_2Cl_2. Yield refers to purified **2** unless otherwise indicated.
[b] Yield refers to purified **4** (10% recovered **1**).
[c] Yield refers to purified **3**.

Compound **2** is obtained as a white crystalline solid. The X-ray structure (Fig. 1) shows an envelope conformation for the oxazolidine ring, the oxygen atom O1 being 0.564(6) Å from the C2 N3 C4 C5 plane defined at ±0.08 Å, thus giving a distance of 2.56 Å for H_{2B} and H_{5A} and 3.52 Å for H_{2B} and H_{4A}.[13] This could explain the difference seen in the NOE spectrum in which there is a much stronger NOE between H_{2B} and H_5 than between H_{2B} and H_4 (Fig. 2). This difference could also be due, in part, to a shield effect of the tosyl group.

With these encouraging results in hand, the next step of our strategy was to introduce a deuterium atom in a stereocontrolled fashion. This was achieved by means of deuterated reducing agents. All the reactions that gave an acceptable yield in Table 1 were tested.

As seen in Table 2, [^{2}H]-Bu_4NBH_4 still gave compound **2** as a single product, but the diastereoselectivity observed was quite disappointing (entry 1). Moreover, temperature has only a minor influence on the stereoselectivity (entry 2) and, to our great surprise, more sterically demanding counterions (such as tetra n-octyl ammonium) gave lower diastereoselectivity (entry 3). Indeed, tributyltin deuteride provided the best result since the reaction gave rise to **2** as a single product with a fairly good isotopic enrichment (>95%) and in a fully diastereoselective fashion (entry 4). Moving to commonly used metallic hydrides for the deuterium or tritium

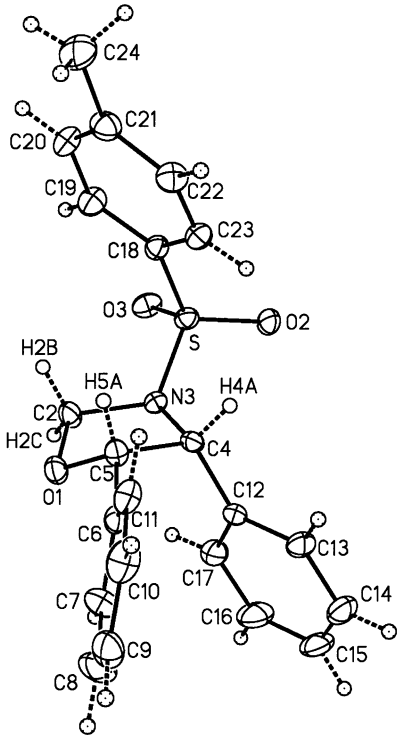


Figure 1. View of compound **2**. Thermal ellipsoids are drawn at the 40% probability level

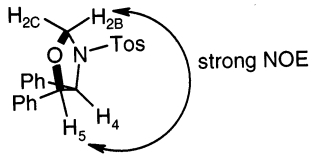


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Figure 2. NOE effects

labelling, [^{2}H]-$NaBH_4$ or [^{2}H]-$NaBH_3CN$ did not give results comparable with those achieved previously using [^{2}H]-Bu_3SnH and $BF_3{\cdot}OEt_2$ (entries 5 and 6). The diastereoselectivity observed during the substitution of the exocyclic methoxy group by deuterides was established on the basis of ^{1}H NMR spectra of compound **2** and [^{2}H]-2 (Fig. 3).

NOE experiments also allowed us to assign the absolute stereochemistry of C2, so in all cases the deuterium atom attacks the postulated intermediate **A** *anti* to the phenyl groups, thus giving (2*S*)-[^{2}H]-**2** as the major diastereomer.[†]

[†] It should be noted that complete epimerization at C2 occurs upon standing of [^{2}H]-**2** in the presence of $BF_3{\cdot}OEt_2$ (2 equivalents) in CH_2Cl_2 (–80°C to room temperature over 6 h).

Table 2
Preparation of [^{2}H]-**2** from **1**

Entry	Deuteride	Time (h)	T (°C)	[^{2}H]-**2**/[^{2}H]-**3**/**4**	D.r.	I.e. (%)[a]	Yield (%)[b]
1	$Bu_4NB^2H_4$	2.5	−60→−45	100/0/0	80/20	90	80
2	$Bu_4NB^2H_4$	4	−80→−60	100/0/0	85/15	85	70
3	$Oct_4NB^2H_4$	4	−80→−60	100/0/0	70/30	89	80
4	Bu_3Sn^2H	4	−80→−40	100/0/0	100/0	>95	85
5	NaB^2H_4	6	−80→−20	51/0/49	85/15	80	43
6	NaB^2H_3CN	24	−80→25	62/8/30	85/15	95	40

[a] Isotopic enrichment of **2**, estimated by ^{1}H NMR.
[b] All reactions performed in CH_2Cl_2 with $BF_3{\cdot}OEt_2$ as Lewis acid. Yield refers to purified **2**.

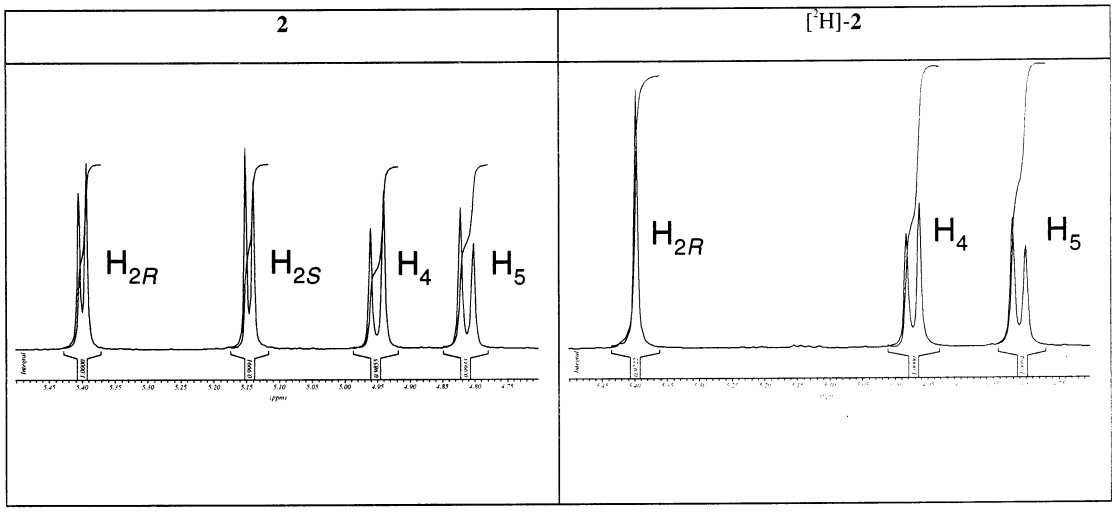

Figure 3. Selected portion of ^{1}H NMR spectrum of **2** and [^{2}H]-**2**

3. Conclusion

In summary, the work described here shows the viability of accessing stereoselectively chiral methylene groups starting from 2-alkoxy oxazolidines. The best conditions that we have found to date are tributyltin deuteride in the presence of $BF_3{\cdot}OEt_2$ with compound **1**, and only one single diastereomer was obtained. Work is now in progress to open the oxazolidine ring, first with nucleophiles to obtain primary chiral amines and then with tritiated hydrides to obtain a chiral methyl group. Our results in both fields will be reported in due course.

4. Experimental

A typical procedure for the preparation of (4*R*,5*S*) 4,5-diphenyl-3-tosyl-1,3-oxazolidine **2** is as follows: 48 μl (0.375 mmol) of $BF_3{\cdot}OEt_2$ was added to a solution of 100 mg (0.25 mmol) of C2 epimeric **1** in 3 ml of anhydrous CH_2Cl_2 at −78°C. The resulting solution was stirred for 15 minutes at −78°C and 100 μl (0.35 mmol) of Bu_3SnH was then added dropwise. The reaction

was monitored by TLC, and when no more starting material could be detected, the reaction mixture was diluted by 20 ml of CH_2Cl_2, quenched with 10 ml of a saturated aqueous solution of NH_4Cl, the aqueous layer was extracted with 2×50 ml of CH_2Cl_2 and the organic phases were combined and dried over Na_2SO_4. After filtration and evaporation of the organic phase, the residue was purified on silica gel (eluent hexane/EtOAc: 75/25, $R_f=0.3$), giving 775 mg (82% yield) of **2** as a white solid. ^{1}H NMR ($CDCl_3$): 2.41 (s, $3H_{Tos}$), 4.81 (d, $1H_5$, $^3J_{1H}=6$), 4.96 (d, $1H_4$, $^3J_{1H}=6$), 5.15 (d, $1H_{2S}$, $^2J_{1H}=3.7$), 5.41 (d, $1H_{2R}$, $^2J_{1H}=3.7$), 6.81–6.85 (m, $4H_{ar}$), 6.97–7.07 (m, $6H_{ar}$), 7.27 (d, $2H_{Tos}$, $^3J_{1H}=7.9$), 7.7 (d, $2H_{Tos}$, $^3J_{1H}=7.9$); ^{13}C NMR ($CDCl_3$): 21.3 (C_{Tos}), 65.1 (C_2), 80.4 (C_5), 84.4 (C_4), 126.3, 127.1, 127.3, 127.5, 127.6, 129.6, 134.28, 134.8, 136.1, 143.8 (C_{ar}); MS (CI/NH_4): 380 (11.8, M+1); 381 (4.2); 396 (11.5); 397 (100, M+18); 398 (35.9); 399 (13); mp 165–166°C; $[\alpha]_D^{25}=-79.6$ ($c=2$, CH_2Cl_2).

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13. Crystal data (deposited at the Cambridge Crystallographic Data Centre): $C_{22}H_{21}NO_3S$, $M=376.46$, hexagonal, $P6_5$, $a=10.104(1)$, $c=33.233(7)$ Å, $V=2938.2(8)$ Å^3, $Z=6$, $\rho_{calcd}=1.287$ g cm^{-3}, $2.4>\theta>23.81°$, μ(Mo Kα)$=0.187$ cm^{-1}, $F(000)=1200$, $T=173$ K. 16 491 reflections collected, 2929 unique, 2241 with $I>2\sigma(I)$, $R=0.0457$. Difference Fourier analysis showed no peaks beyond 0.16 or –0.23 e Å^{-3}. Data were recorded on a Nonius Kappa-CCD area-detector diffractometer using graphite-monochromatized Mo Kα radiation. The crystal-to-detector distance was set to 32 cm and the unit cell was determined from all the reflections measured on 10 frames

with Φ rotation steps of 2°. A 180° Φ range was scanned during data recording (90 frames, Φ rotation = 2°, exposure time = 20 s by frame). The data were processed with the HKL package (Otwinowski, Z.; Minor, W. *Methods Enzymol*. **1997**, *276*, 307), the structure was solved by direct method and subsequent Fourier difference with SHELXS-86 (G.M. Sheldrick, SHELXS-86, Program for the Solution of Crystals Structures, University of Göttingen, Germany, 1990) and refined on F^2 with SHELXTL (G.M. Sheldrick, SHELXTL, Version 5.1, University of Göttingen, Germany, distributed by Bruker AXS, Madison, Wisconsin, 1999) with anisotropic thermal parameters. H atoms were introduced at calculated positions as riding atoms with an anisotropic displacement parameter equal to 1.2 (CH, CH_2) or 1.5 (CH_3) times that of the parent atom.