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A chiral 1,4-oxazin-2-one: asymmetric synthesis versus resolution, structure, conformation and VCD absolute configuration

A. Solladié-Cavallo,[a,*] O. Sedy,[a,b] M. Salisova,[b,†] M. Biba,[c] C. J. Welch,[c,‡] L. Nafié[d,§] and T. Freedman[d,¶]

[a]*ECPM/Universitè Louis Pasteur, 67087 Strasbourg, France*
[b]*Department of Organic Chemistry, Comenius University, 842 15 Bratislava, Slovakia*
[c]*Merck & Co., Inc., Rahway, NJ 07065, USA*
[d]*Department of Chemistry, Syracuse University, Syracuse, New York, NY 13244-4100, USA*

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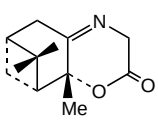
Abstract—1,4-Oxazin-2-one **3** is obtained from 2-pinanone in 4 steps and 78% overall yield. Enantiopure (e.e. >99%) (*R*)-(+)-**3** and (*S*)-(−)-**3** were obtained through chiral supercritical fluid chromatography (using a semi preparative Chiralpak AS column) with almost quantitative recovery of material. The structure and the boat-conformation of the lactone ring have been determined by NMR and the absolute configuration determined by VCD.

1. Introduction

The chiral 1,4-oxazinone **1**, derived from hydroxypinanone was synthesized by Viallefont et al. in 1988[1,2] and has been shown to give dialkylation reactions as well as dehydrated aldol products.[3] The structurally similar, but less constrained oxazinone **2** was proposed in 2000 by Najera et al.[4] and the propensity of **2** to give dehydrated aldol products was also studied.

We present herein the synthesis, the structure and conformation determination by NMR, resolution using supercritical fluid technique and VCD determination of the absolute configuration of the chiral oxazinone **3**.



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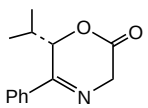

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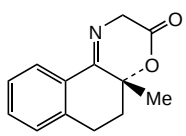

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2. Results and discussion

2.1. Synthesis

It is well known that methylation of 1-tetralone through the lithium enolate generated with LDA leads to low yields (~45%).[5] However, by using a 'naked' enolate generated with *t*-BuP_4,[6] 1-tetralone was quantitatively methylated with MeI. The phosphazene base (*t*-BuP_4) can be recovered by isolation (through precipitation with hexane) of the hydro-iodide salt formed. Asymmetric hydroxylation of **4** using Davis' reagent,[7] (1*S*)-(+)-(8,8-dichlorocamphorsulfonyl)-oxaziridine **5** was tried; but, although the yield in **6** (83%) was satisfying, only 90/10 e.r. was obtained. Therefore, racemic oxazinone **3** was prepared[8] and then resolved. It is worth noting that formation of **3** occurs spontaneously upon reaction of **6** with methyl glycinate in benzene at reflux in the presence of traces of $BF_3{\cdot}OEt_2$. The conversion is quantitative and pure **3** was isolated in 96% yield (Scheme 1).

2.2. Structure and conformation of 3

2.2.1. NMR. No signal was observed which would correspond to an ester–MeO but only one singlet corresponding to the expected Me–C (1.55 ppm). The CH_2 of the lactone ring exhibits a non-equivalence of 0.5 ppm in $CDCl_3$ (d at 4.35 ppm and d at 4.85 ppm) and

* Corresponding author. E-mail: ascava@ecpm.u-strasbg.fr
† salisova@fns.uniba.sk
‡ christopher_welch@merck.com
§ lnafie@syr.edu
¶ tbfreedm@syr.edu

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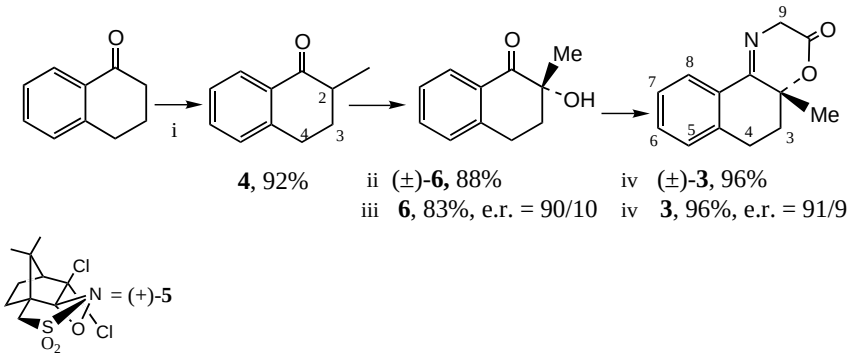

Scheme 1. (i) *t*-BuP_4 1 M in hexane, MeI, −78°C, THF; (ii) TMSCl/Et_3N/NaI, MeCN/pentane, 25°C; *m*-CPBA/$NaHCO_3$, CH_2Cl_2, HCl, 25°C; (iii) NHMDS 1 M in THF, −78°C, **5**, THF; (iv) $H_2NCH_2CO_2Me$, trace $BF_3{\cdot}OEt_2$, benzene, reflux.

a NOESY experiment shows that the methyl is correlated with one H of the lactone ring CH_2 (d at 4.35 ppm), as expected for a lactone ring in a boat-form and with a methyl axial. Therefore, an axial position was assigned to this proton at 4.35 ppm (d). Moreover, one of the aromatic doublets (7.23 ppm) was correlated to the CH_2 multiplet at 3.05 ppm, which was thus assigned to the benzylic protons. It is worth noting that the 22 Hz value observed for the geminal coupling constant on the lactone CH_2 is consistent with the boat conformation of this ring, as, in this conformation, the lactone–carbonyl bisects the CH_2 dihedral angle leading to a maximum π-neighboring effect.[9]

The boat conformation of the lactone ring (origin of the large non-equivalence of the CH_2 protons) led us to expect a very acidic compound with a strong π.σ*-hyperconjugative interaction between one of the C–H bonds and the π-system of the carbonyl as well as good stereodifferentiation because of an expected preferred pseudo-equatorial substituent at this position.

The enantiomeric ratio of **3** (obtained from enriched **6**) was determined to be 91/9 by ^{1}H NMR (400 MHz, $CDCl_3$) using $Eu(hfc)_3$. A splitting of the methyl-singlet (at 1.55 ppm) and of the doublet (at 4.85 ppm) of the equatorial-H of the lactone ring–CH_2 was rapidly observed. In the major enantiomer, the methyl singlet is shielded, while the H-equatorial doublet is deshielded (compared to the minor isomer). An enantiomeric ratio of 90/10 was found for the starting hydroxyketone **6** using ^{1}H NMR (400 MHz, $CDCl_3$) and the same $Eu(hfc)_3$ complex (splitting of the methyl singlet). It thus appeared that the asymmetric induction during hydroxylation was much lower than expected from literature results.[7]

2.3. Resolution of (±)-3 via chiral HPLC

Resolution of (±)-**3** was carried out by supercritical fluid chromatography and a semi-preparative Chiralpak AS column (2×25 cm, ChiralTechnologies, Exton, PA) operating at a flow rate of 50 mL/min with a mobile phase of 8% methanol in carbon dioxide (100 bar outlet pressure). Detection was done by UV at 300 nm. Injection of 1 mL of (±)-**3** as a 25 mg/mL solution in methanol afforded the baseline resolution of both enantiomer in less than 10 min. A total of 150 mg of (±)-**3** was resolved with both enantiomers being obtained in >99% e.e. with good recovery (93% for the first eluted and 89% for the second).

Circular dichroism measurements (0.06 mg/mL in methanol) indicated a negative CD signal at 300 nm for the first eluted enantiomer ($[\alpha]_D^{20} = -298$, $CHCl_3$) and a positive signal at this wavelength for the second eluted enantiomer.

2.4. Absolute configuration determination by VCD

The absolute configuration of **3** was determined by comparing the measured VCD[10–16] spectrum of a sample of (+)-**3** having an e.r. of 91/9 and ∼100% chemical purity with that of a DFT quantum calculation of the VCD spectrum of the (*R*)-isomer. The sample was dissolved in $CDCl_3$ and placed in a 100 μm path length cell with BaF_2 windows. The VCD and IR spectra were collected on a modified Chiral*ir* VCD spectrometer (ABB Bomem/Biotools) at 4 cm^{-1} resolution with the instrument optimized for 1400 cm^{-1}, with a 2 h collection for the VCD.[17] Isomer (*R*)-**3** was first constructed with HyperChem (Hypercube, Inc.), and calculation of the optimized geometry (Fig. 1), vibrational frequencies, normal modes, IR and VCD intensities were carried out at the DFT B3LYP/6-31G* level with Gaussian 98.

It is worth noting that the conformation found by calculation corresponds to the conformation found by NMR with a methyl axial and the iminolactone ring in a boat shape.

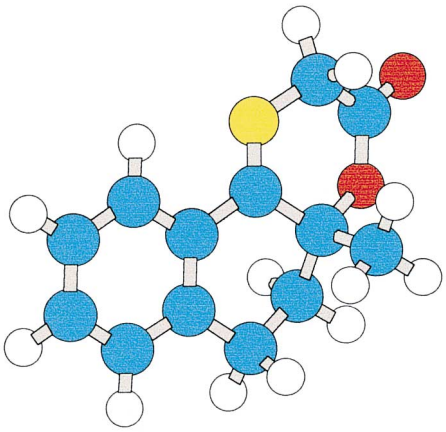

Figure 1. Optimized geometry of (*R*)-**3**.

The calculated IR and VCD spectra are compared to experiment in Fig. 2. The excellent agreement between experiment and calculation establishes the absolute configuration of the sample studied as *R*, and also indicates that the conformer calculated is the predominant one in solution in $CDCl_3$.

3. Conclusion

In conclusion, the resolution which provides both enantiomers of iminolactone **3** in high yield and high e.r. is more efficient that the asymmetric synthesis which provides the desired compound in only 91/9 e.r. It has also been determined by VCD that the second eluted enantiomer (+, $CHCl_3$)-**3** has *R* configuration.

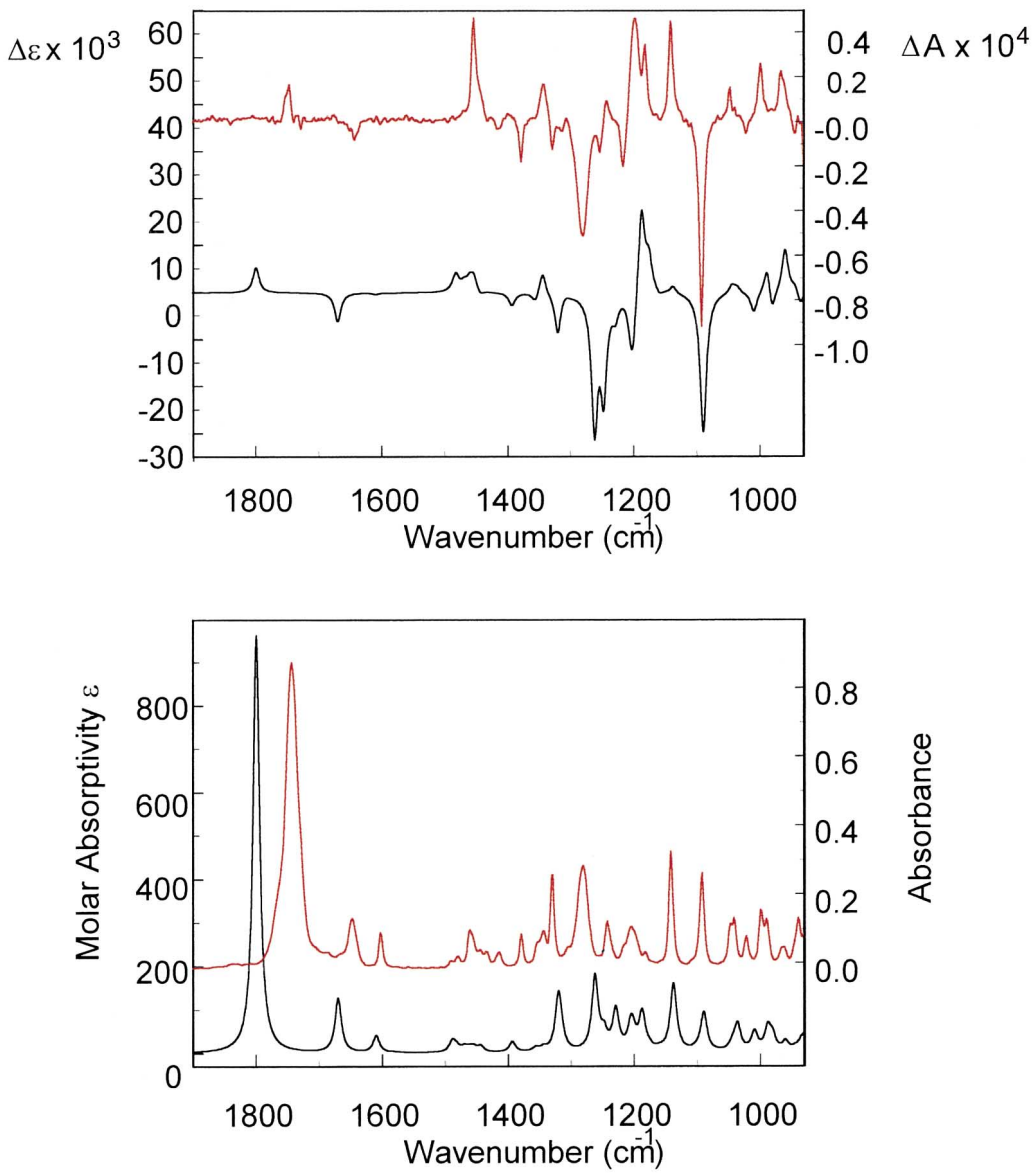

Figure 2. Comparison of observed VCD and IR spectra of a sample of (+, $CHCl_3$)-**3** with calculated VCD and IR spectra of geometry-optimized (*R*)-**3**. (red: observed; black: calculated).

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) and 2D-COSY on a Bruker Avance (400 MHz) spectrometer with $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm downfield from TMS and coupling constants (J) in Hz.

The resolution was carried out using a semi preparative SFC instrument from Berger Instrument, Newark, DE. Circular dichroism measurements were performed on a Jasco 810 instrument. TLC were performed on Merck's glass plates with silica gel 60 F_{254}. Silica gel Si 60 (40–60 μm) from Merck was used for the chromatographic purifications. α-Tetralone, sodium bis(trimethylsilyl)-amide, 1m solution of t-BuP_4 in hexane and (1*S*)-(+)-(8,8-dichlorocamphorsulfonyl)-oxaziridine were purchased from Aldrich, Aldrich, Fluka and Fluka, respectively, and used without further purification. Usual IR spectra and rotations were recorded/determined on a Perkin–Elmer Spectrum one and a Perkin–Elmer 341, respectively.

For VCD determination of absolute configuration, infra red absorption and VCD spectrum were recorded in a 100 mm pathlength BaF_2 cell, at 4 cm^{-1} resolution, using Chiral*ir* Fourier transform VCD spectrometer from ABB Bomem/BioTools (Quebec, Canada) optimized for operation at 1400 cm^{-1}. VCD spectrum was recorded for 2 h by co-adding approximately 4800 interferometric scans. The sample was dissolved in $CDCl_3$ (80 mg/mL).

4.2. 2-Methyl-1-tetralone (2-methyl-3,4-dihydro-2*H*–naphthalen-1-one) 4

To a stirred solution of 1-tetralone (21 mg, 0.14 mmol, 1 equiv.) in anhydrous THF (2 mL) was added dropwise the phosphazene base t-BuP4 (0.14 mL of 1 M soln in hexane, 0.14 mmol, 1 equiv.) at −78°C under argon. After stirring for 20 min at the same temperature, iodomethane (36 μL, 0.57 mmol, 4 equiv.) was added dropwise. Reaction mixture was then stirred at −78°C for 0.5 h, while monitoring the by TLC (hexane/ethyl acetate 4:1). When the reaction was complete, the solvent was evaporated and the crude product was chromatographed on silica gel (hexane/EtOAc, 50/1). Isolated yield: 21 mg, (92%) colorless oil. ^{1}H NMR: ($CDCl_3$) δ 1.28 (3H, d, ^3J=6.5, CH_3), 1.91 (1H, dddd, ^2J=13, ^3J=12, ^3J=11, ^3J=4.5, H_{3a}), 2.23 (1H, dq, ^2J=13, three times ^3J=4.5, H_{3e}), 2.62 (1H, ddq, ^3J=12, ^3J=4.5, three times ^3J=6.5, H_2), 3.00 (1H, dt, ^2J=16.5, twice ^3J=4.5, H_{4e}), 3.07 (1H, ddd, ^2J=16.5, ^3J=11, ^3J=4.5, H_{4a}), 7.25 (1H, d, ^3J=7.5, H_5), 7.32 (1H, t, ^3J=7.5, H_7), 7.46 (1H, dt, ^3J=7.5, ^4J=1.5, H_6), 8.19 (1H, dd, ^3J=7.5, ^4J=1.5, H_8). ^{13}C NMR: ($CDCl_3$) δ 15.5 (CH_3), 28.9 (CH_2), 31.5 (CH_2), 42.7 (CH), 126.6 (CH), 127.5 (CH), 128.8 (CH), 132.5 (C), 133.2 (CH), 144.3 (C), 200.9 (C=O); IR: $\nu_{C=O}$=1684 cm^{-1}. Anal. for $C_{11}H_{12}O$: C, 82.46; H, 7.55; found C, 81.45; H, 7.55%

4.3. 2-Hydroxy-2-methyl-1-tetralone (2-hydroxy-2-methyl-3,4-dihydro-2*H*–naphthalen-1-one) 6

To a stirred solution of 2-methyl-1-tetralone (0.913 g, 5.7 mmol, 1 equiv.) in anhydrous THF (10 mL) was added dropwise a solution of NHMDS (sodium bis(trimethylsilyl)amide) (1 M soln in THF, 6.84 mL, 6.84 mmol, 1.2 equiv.) at −78°C under argon. After stirring for 0.5 h at −78°C, a precooled solution (−78°C) of oxaziridine **5** (2.09 g, 6.84 mmol, 1.2 equiv.) in anhydrous THF (10 mL) was added dropwise to the reaction mixture at −78°C and stirring was maintained for 1 h at the same temperature. The reaction was quenched at −78°C by addition of saturated NH_4Cl solution (1 mL). The temperature was allowed to increase to 20°C and solvents were evaporated under vacuum. The crude product was dissolved in dichloromethane (30 mL), NH_4Cl was filtered off (frite 4), washed with access of CH_2Cl_2 and the solvent of the combined organic phases was evaporated under vacuum. The residue was chromatographed on silica gel (hexane/EtOAc, 9/1). Isolated yield: 828 mg (83%) colorless oil. ^{1}H NMR: ($CDCl_3$) δ 1.42 (3H, s, CH_3), 2.24 (1H, ddd, ^2J=13, ^3J=11.5, ^3J=5.5, CH_{3a}), 2.29 (1H, ddd, ^2J=13, ^3J=6, ^3J=3, CH_{3e}), 3.05 (1H, ddd, ^2J=18, ^3J=5.5, ^3J=3.5, CH_{4e}), 3.13 (1H, ddd, ^2J=18, ^3J=12, ^3J=6, CH_{4a}), 3.86 (1H, bs, OH), 7.28 (1H, dd, ^3J=7.5, ^4J=1.5, H_5), 7.37 (1H, dt, ^3J=7.5, 7.5, ^4J=1.5, H_7), 7.54 (1H, dt, ^3J=7.5, 7.5, ^4J=1.5, H_6), 8.19 (1H, dd, ^3J=7.5, ^4J=1.5, H_8). ^{13}C NMR: ($CDCl_3$) δ 24.0 (CH_3), 26.9 (CH_2), 36.0 (CH_2), 73.7 (C-OH), 127.0 (CH), 128.1 (CH), 129.1 (CH), 134.2 (C), 134.2 (CH), 143.5 (C), 201.9 (C=O). IR: $\nu_{C=O}$=1689 cm^{-1}, ν_{OH}=3480 cm^{-1}. Anal. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found C, 74.35; H, 6.94. $[\alpha]_D^{20}$=+10 (c=0.45, $CHCl_3$), e.r.=90/10, from asymmetric hydroxylation. (±)-**6** has been prepared through m-CPBA oxidation of the silyl enol ether of ketone **4**, followed by TBAF hydrolysis (yield=88% from **4**).[8]

4.4. Iminolactone, 3

To a stirred solution of 2-hydroxy-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one (47 mg, 0.27 mmol, 1 equiv.) in dry benzene (2 mL) was added BF_3–etherate (1 drop, catalytic amount) at room temperature under argon. After 10 min stirring at room temperature methyl glycinate (2 equiv., 48 mg, 0.54 mmol) in dry benzene (2 mL) was added and the reaction mixture was stirred under reflux for 2 h with a Dean–Stark trap. A second portion of methylglycinate (2 equiv., 48 mg, 0.54 mmol) in dry benzene (2 mL) was added and reflux continued for 2 h; a third portion of methyl glycinate (1 equiv., 24 mg, 0.27 mmol) in dry benzene (1 mL) was added and reflux continued for a further 12 h. The progress of the reaction was monitored by TLC (hexane/ethyl acetate, 4/1). The temperature was allowed to decrease to room temperature, solvent was evaporated and the crude product was purified by chromatography (hexane/EtOAc, 9/1). Isolated yield: 54 mg (96%), white crystals: mp 123–127°C. ^{1}H NMR: ($CDCl_3$) δ 1.56 (3H, s, CH_3), 2.29 (2H, m, CH_2 at C(3)), 3.05 (2H, m, CH_2 at C(4)), 4.35 (1H, d, ^2J=22, O=C-CH_{axial}-N=), 4.85 (1H,

d, $^2J=22$, O=C-$CH_{equat.}$-N=), 7.23 (1H, bd, $^3J=7.5$, H_5), 7.32 (1H, bt, $^3J=7.5$, H_7), 7.42 (1H, dt, $^3J=7.5$, 7.5, $^4J=1.5$, H_6), 8.19 (1H, dd, $^3J=7.5$, $^4J=1.5$, H_8). ^{13}C NMR: ($CDCl_3$) δ 21.4 (CH_3), 26.7 (CH_2), 35.1 (CH_2), 50.5 (CH_2N), 80.9 (C-O), 126.0 (CH), 127.2 (CH), 128.9 (CH), 130.3 (C), 131.6 (CH), 138.3 (C), 165.2 (C=O), 168.3 (C=N). IR: $\nu_{COlactone}=1749$ cm^{-1}, $\nu_{C=N}=1650$ cm^{-1}. Anal. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; found C, 72.89; H, 6.15. $[\alpha]_D^{20}=+240$ ($c=1$, $CHCl_3$), e.r. = 91.5/8.5 (through asymmetric hydroxylation). $[\alpha]_D^{20}=-298$ ($c=1$, $CHCl_3$), e.r. = 99.5/0.5 (through resolution).

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