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Synthesis and determination of the absolute stereochemistry of the enantiomers of adrafinil and modafinil

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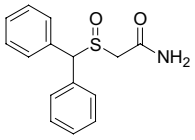
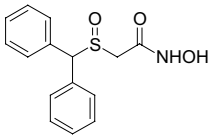
Abstract—Both enantiomers of modafinil, adrafinil, modafinic acid and ethyl modafinate were prepared from the diastereomers formed by reacting racemic β-sulfinyl carboxylic acid with (4*R*)-phenyl-thiazolidinethione. The absolute stereochemistry of the sulfoxide group was confirmed via X-ray analysis of one of the thiazolidinethione diastereomers.

1. Introduction

Modafinil [Provigil] (±)-**1** is a psychostimulant used in the treatment of narcolepsy.[1] Adrafinil [Olmifon] (±)-**2**, the hydroxamic acid derivative of modafinil, is currently in phase III clinical trials for the same disorder. Recent work has suggested that **1** and **2** might also be effective treatments for ADHD as well as treating opioid-induced sedation.[2,3] The exact mechanisms through which (±)-**1** and (±)-**2** exert their effects are currently unclear. However, its mechanism of action appears different from that of other CNS stimulants such as *d*-amphetamine.[4–6] Given their unique pharmacological properties, clinical work has begun to explore the utility of these agents as pharmacological treatments for stimulant dependence.[7]



Modafinil **1**



Adrafinil **2**

Modafinil **1** and adrafinil **2** each possess a stereogenic sulfoxide group, however, they are marketed as racemic materials. Recently, Prisinzano et al. reported the diastereomeric salt resolution of a β-sulfinyl carboxylic acid with each of the two enantiomers of α-methylbenzylamine.[8] This method provided the enantiomeric forms of β-sulfinyl carboxylic acid **4** in less than 21% yield and 44%, respectively. In order to improve the preparation of both enantiomeric forms of modafinil and adrafinil, we selected a chiral thiazolidinethione auxiliary to carry out a chemical resolution of the β-sulfinyl carboxylic acid. The chiral auxiliary was selected to provide two enantiomerically pure synthetic intermediates in one single operation. Herein, we report our results and also confirm the absolute stereochemistry of the enantiomeric forms via X-ray analysis of one of the diastereomeric thiazolidinethione derivatives.

2. Results and discussion

We selected an aminoacid-derived thiazolidinethione as the chiral auxiliary for the resolution of a racemic mixture of β-sulfinyl carboxylic acid **4** based on our experience with these versatile molecules (Scheme 1).[9] Diastereomeric mixtures with chiral thiazolidinethiones can be easily separated by column chromatography because of their different R_f values, their yellow colour and also the ability to recycle the silica gel. These chiral auxiliaries have also proved superior to others, because they are easily displaced by several nucleophilic reagents.[10]

Chiral thiazolidinethione auxiliary (−)-**3**,[11] derived from phenyl glycine, was coupled with racemic sulfinyl carboxylic acid **4** (Scheme 1),[12,13] and the two diastereomeric

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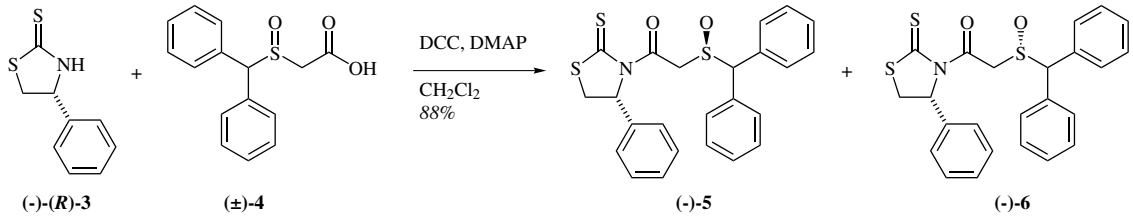


Scheme 1. Resolution of β-sulfinyl carboxylic acid **4**.

products were easily separated by column chromatography. An X-ray crystallographic analysis of diastereomer (−)-**5** showed the absolute stereochemistry of the sulfinyl group to be *R* (Fig. 1).[14] Thus, the stereochemistries of the sulfinyl groups in the two diastereomers were unequivocally assigned as illustrated in Scheme 1.

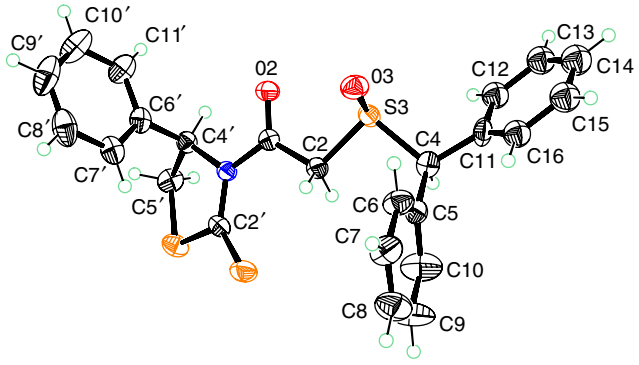
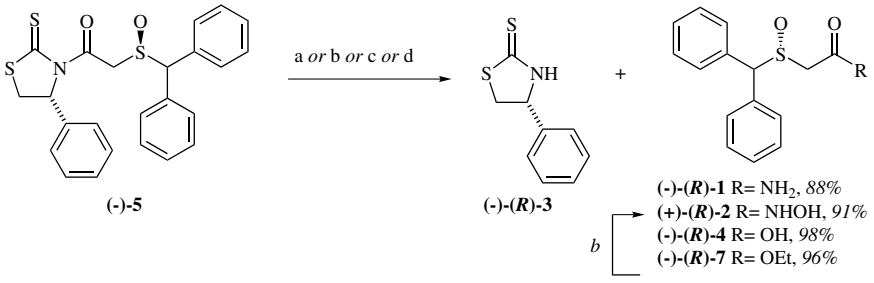


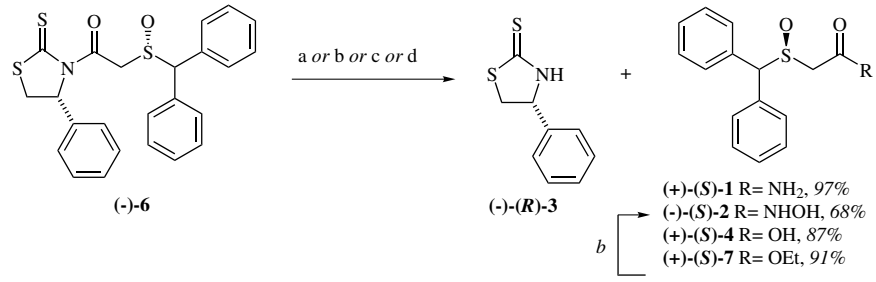
Figure 1. X-ray crystal structure of compound (−)-**5**.

With both diastereomers in hand, our efforts shifted to the preparation of adrafinil. Diastereomeric thiazolidinethione **5** was treated with a solution containing a mixture of chloroform–methanol and ammonium hydroxide (78:20:2) (Scheme 2). The reaction was monitored by TLC; when no more starting material was observed, the solvent was evaporated and the resulting mixture of chiral auxiliary and modafinil separated by silica gel column chromatography. Modafinil (−)-(*R*)-**1** was obtained in very good yield while chiral thiazolidinethione was also recovered. The same thiazolidinethione **5** was then treated with hydroxylamine hydrochloride to yield adrafinil (+)-(*R*)-**2** in 91% yield. It is noteworthy that this method provides the desired targets directly from the diastereomeric thiazolidinethiones and the chiral auxiliaries can be recovered and recycled. Thiazolidinethione **5** was also hydrolyzed and esterified to show its synthetic versatility. Adrafinil (+)-(*R*)-**2** was also obtained from ethyl modafinate (−)-(*R*)-**7** in moderate yield (75%).

In the same manner, the addition of ammonia to diastereomeric thiazolidinethione **6** yielded modafinil (+)-(*S*)-**1**, while the addition of hydroxylamine to compound **6** furnished adrafinil (−)-(*S*)-**2**, both in excellent yields (Scheme 3). Hydrolysis of thiazolidinethione **6** delivered



Scheme 2. Synthesis of (*R*)-modafinil and (*R*)-adrafinil. Reagents: (a) $CHCl_3$–MeOH–NH_4OH (78:20:2); (b) NH_2OH–HCl, Et_3N, THF–H_2O; (c) LiOH, THF–H_2O; (d) DCC, EtOH.



Scheme 3. Synthesis of (*S*)-modafinil and (*S*)-adrafinil. Reagents: (a) NH_4OH–MeOH–$CHCl_3$ (78:20:2); (b) NH_2OH–HCl, Et_3N, THF–H_2O; (c) LiOH, THF–H_2O; (d) DCC, EtOH.

modafinic acid (+)-(*S*)-**7**, and esterification furnished ethyl modafinate (+)-(*S*)-**7**.

3. Conclusions

In summary, we have prepared both enantiomers of modafinil, adrafinil, modafinic acid and ethyl modafinate employing a chemical resolution of a diastereomeric mixture formed by reacting racemic β-sulfinyl carboxylic acid with a chiral thiazolidinethione. The absolute stereochemistry of the sulfoxide group was confirmed via X-ray analysis of one of the thiazolidinethione diastereomers. Thiazolidinethiones were shown to be easily displaced by ammonia and hydroxylamine providing modafinil and adrafinil in one operation. This strategy will be useful to prepare other analogues to further explore the pharmacological activity of these compounds. The biological evaluation of these single enantiomeric compounds is currently underway and will be reported in due course.

4. Experimental

4.1. General remarks

Melting points were determined on Thomas Hoover apparatus. Optical rotations were measured on a Jasco P-1020 polarimeter at room temperature. NMR spectra were recorded in a Bruker Avance-300 spectrometer. IR spectra were recorded on a Nicolet-210 spectrophotometer. HRMS was conducted by Dr. Blake Watkins at the University of Mississippi.

4.2. Coupling of thiazolidinethione 3 and carboxylic acid 4

A solution of (−)-(*R*)-phenylthiazolidinethione (410.2 mg, 2.1 mmol) in dichloromethane (15 mL) was treated with racemic modafinic acid (548.6 mg, 2.0 mmol). 4-Dimethylaminopyridine (45 mg, 0.37 mmol) and 1,3-dicyclohexylcarbodiimide (454 mg, 2.2 mmol) were then added under a nitrogen atmosphere. The solution was stirred overnight. The reaction was quenched with a 2 M solution of hydrochloric acid (20 mL) and extracted with diethyl ether (2 × 25 mL). The combined organic layers were washed with a satd solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (5 × 13 cm) eluting with petroleum ether–ethyl acetate (3:2). Thiazolidinethione **5** was obtained as a yellow solid: 403 mg (44.5% yield) with thiazolidinethione **6** was obtained as a yellow foam: 395 mg (43.5% yield).

4.2.1. (−)-[(4*R*)-Phenyl-2-thioxo-thazolidine-3-yl]-(*R*)-(diphenylmethanesulfinyl)acetamide (−)-5. R_f 0.38 (3:2, petroleum ether/ethyl acetate); mp 134–136 °C (dec); $[\alpha]_D^{22} = -230.4$ (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.53–7.27 (15H, m), 6.13 (1H, dd, $J = 8.1$, 1.2 Hz), 5.20 (1H, s), 5.10 (1H, d, $J = 14.2$ Hz), 4.13 (1H, d, $J = 14.2$ Hz), 3.93 (1H, dd, $J = 11.2$, 8.1 Hz), 3.09 (1H, dd, $J = 11.2$, 1.2 Hz); ^{13}C NMR ($CDCl_3$): δ 202.7 (C), 165.4 (C), 138.5 (C), 135.3 (C), 134.1 (C), 129.65 (2CH), 129.29 (2CH), 129.16 (2CH), 129.07 (2CH), 128.93 (2CH), 128.72 (CH), 128.67 (CH), 128.57 (CH), 125.4 (2CH), 71.8 (CH), 69.71 (CH), 57.5 (CH_2), 37.2 (CH_2); IR *v* 1677, 1495, 1450, 1357, 1304, 1248, 1170, 1158, 1045 cm^{-1}; ES HRMS *m/z* $(M+H)^+$ calcd 452.0813, obsd 452.0821.

4.2.2. (−)-[(4*R*)-Phenyl-2-thioxo-thazolidine-3-yl]-(*S*)-(diphenylmethanesulfinyl)acetamide (−)-6. R_f 0.24 (3:2, petroleum ether/ethyl acetate); mp 69 °C (dec); $[\alpha]_D^{22} = -216.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.49–7.29 (15H, m), 6.17 (1H, d, $J = 8.1$ Hz), 5.07 (1H, s), 4.55 (1H, d, $J = 16.0$ Hz), 4.28 (1H, d, $J = 16.0$ Hz), 3.96 (1H, dd, $J = 11.2$, 8.1 Hz), 3.09 (1H, dd, $J = 11.2$, 1.1 Hz); ^{13}C NMR ($CDCl_3$): δ 202.6 (C), 165.8 (C), 138.5 (C), 135.7 (C), 133.9 (C), 129.77 (2CH), 129.40 (2CH), 129.23 (2CH), 129.01 (2CH), 128.94 (2CH), 128.89 (CH), 128.77 (CH), 128.61 (CH), 125.7 (2CH), 71.5 (CH), 69.6 (CH), 59.7 (CH_2), 37.3 (CH_2); IR *v* 3063, 3028, 3004, 1694, 1495, 1451, 1299, 1160, 1046, 743, 697 cm^{-1}; ES HRMS *m/z* $(M+H)^+$ calcd 452.0813, obsd 452.0818.

4.2.3. (−)-(*R*)-(Diphenylmethanesulfinyl)acetamide (−)-(*R*)-1. A mixture of chloroform–methanol, ammonium hydroxide (78:20:2, 5 mL) was added directly to thiazolidinethione (−)-**5** (179 mg, 0.396 mmol). The solution was stirred until the yellow colour disappeared and TLC did not show the presence of starting material. The solvent was evaporated and the residue purified by column chromatography (2.5 × 12.5 cm) eluting with a gradient of 1–4% methanol in dichloromethane. Modafinil was obtained as a white solid: 95 mg (88% yield). R_f 0.30 (5% methanol in dichloromethane); mp 158–159 °C; $[\alpha]_D^{22} = -79$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.51–7.48 (2H, m), 7.45–7.32 (8H, m), 7.07 (1H, br s), 5.88 (1H, br s), 5.24 (1H, s), 3.47 (1H, d, $J = 14.2$ Hz), 3.14 (1H, d, $J = 14.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 166.5 (C), 134.7 (C), 134.3 (C), 129.62 (2CH), 129.58 (2CH), 129.1 (2CH), 128.98 (3CH), 128.8 (CH), 71.6 (CH), 52.0 (CH_2); IR 3383, 3314, 3257, 3191, 1690, 1617, 1495, 1376, 1027, 702 cm^{-1}; ES HRMS *m/z* $(M+Na)^+$ calcd 296.0721, obsd 296.0713.

4.2.4. (+)-(*S*)-(Diphenylmethanesulfinyl)acetamide (+)-(*S*)-1. The title compound was obtained in 97% yield from compound (−)-**6** following the same procedure as above. $[\alpha]_D^{22} = +81$ (*c* 1.0, $CHCl_3$).

4.2.5. (+)-(*R*)-(Diphenylmethanesulfinyl)acetohydroxamic acid (+)-(*R*)-2. To a solution of hydroxylamine-hydrochloride (578.6 mg, 8.3 mmol) in a mixture of THF–H_2O (10 mL, 5:1) was added triethylamine (1.5 mL, 10.7 mmol). The mixture was stirred for 15 min, filtered through a small plug of cotton and added to a solution of thiazolidinethione (−)-**5** (376.1 mg, 0.83 mmol). The solution was stirred until no more starting material was observed by TLC. The solution was concentrated and the residue purified by column chromatography on silica gel (2 × 13 cm), eluting with a gradient using 2–6% methanol in dichloromethane. Adrafinil was

isolated as a slightly brown solid: 218.5 mg (91% yield). R_f 0.42 (10% MeOH in $CHCl_3$); mp 159–160 °C; $[\alpha]_D^{22} = +14$ (*c* 0.85, CH_3OH); ^1H NMR (CD_3OD): δ 7.56–7.51 (4H, m), 7.44–7.32 (6H, m), 5.40 (1H, s), 3.41 (1H, d, $J = 13.7$ Hz), 3.23 (1H, d, $J = 13.7$ Hz); ^{13}C NMR (CD_3OD): δ 163.5 (CO), 137.2 (C), 135.6 (C), 130.9 (2CH), 130.3 (2CH), 129.9 (2CH), 129.8 (2CH), 129.6 (2CH), 72.1 (CH), 54.0 (CH_2); IR 3209, 3027, 1686, 1656, 1496, 1451, 1061, 1005, 703 cm^{-1}; ES HRMS *m/z* $(M+Na)^+$ calcd 312.0670, obsd 312.0659.

4.2.6. (−)-(*S*)-(Diphenylmethanesulfinyl)acetohydroxamic acid (−)-(*S*)-2. The title compound was obtained in 98% yield from compound (−)-**6** following the same procedure as above. $[\alpha]_D^{22} = -14$ (*c* 1.0, CH_3OH).

4.2.7. (−)-(*R*)-(Diphenylmethanesulfinyl)acetic acid (−)-(*R*)-4. A 0.1 M THF/H_2O (2.5:1) solution of LiOH (15 mL, 1.5 mmol) was added to thiazolidinethione imide (−)-**5** (180 mg, 0.398 mmol) at 0 °C. The solution was then stirred at room temperature until no imide was observed by TLC. Water (15 mL) was added to solution and washed with dichloromethane (4 × 10 mL). The aqueous solution was acidified (1 mL of concd HCl) and extracted with ethyl acetate (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The title compound was obtained as an amorphous solid: 105 mg (96% yield). R_f 0.21 (10% MeOH in $CHCl_3$); mp 118–120 °C; $[\alpha]_D^{22} = -41.7$ (*c* 0.85, CH_3OH); ^1H NMR ($CDCl_3$): δ 7.56–7.51 (4H, m), 7.44–7.32 (6H, m), 5.40 (1H, s), 3.41 (1H, d, $J = 13.7$ Hz), 3.23 (1H, d, $J = 13.7$ Hz); ^{13}C NMR (acetone-d_6): δ 167.3 (CO), 137.6 (C), 135.8 (C), 129.8 (2CH), 129.1 (2CH), 128.7 (2CH), 128.5 (2CH), 128.2 (CH), 128.1 (CH), 71.4 (CH), 55.4 (CH_2); IR 2925, 2778, 2527, 1716, 1500, 1451, 1287, 1187, 1016, 750, 704 cm^{-1}; ES HRMS *m/z* $(M+Na)^+$ calcd 297.0561, obsd 297.0559.

4.2.8. (+)-(*S*)-(Diphenylmethanesulfinyl)acetic acid (+)-(*S*)-4. The title compound was obtained in 87% yield from compound (−)-**6** following the same procedure as above. $[\alpha]_D^{22} = +39.3$ (*c* 1.0, CH_3OH).

4.2.9. (−)-(*R*)-Ethyl (diphenylmethanesulfinyl)acetate (−)-(*R*)-7. A solution of thiazolidinethione imide (−)-**5** (242 mg, 0.53 mmol) in ethanol (10 mL), was treated with dicyclohexylcarbodiimide (166.2 mg, 0.80 mmol) and 4-dimethylaminopyridine (6 mg, 0.05 mmol). The solution was stirred until the yellow colour disappeared and TLC showed no more starting material. The solvent was evaporated, and the residue purified by column chromatography on silica gel (2 × 12 cm), eluting with petroleum ether–ethyl acetate (55:45). The ethyl ester (−)-**7** was eluted after the phenyl-thiazolidinethione and obtained as a white paste: 158.4 mg (98% yield). R_f 0.23 (7:3, petroleum ether–ethyl acetate); mp 84–85 °C; $[\alpha]_D^{22} = -58.5$ (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.52–7.46 (4H, m), 7.43–7.30 (6H, m), 5.20 (1H, s), 4.20 (2H, q, $J = 7.2$ Hz), 3.51 (1H, d, $J = 14.0$ Hz), 3.99 (1H, d, $J = 14.0$ Hz), 1.28 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (CD_3OD): δ 165.5 (CO), 135.5 (C), 134.0 (C), 129.8 (2CH), 129.4 (2CH), 128.9 (4CH), 128.7 (CH), 128.6 (CH), 71.6 (CH), 62.2 (CH_2), 54.4 (CH_2), 14.2 (CH_3); IR 3061, 3029, 2983, 2932, 1732, 1495, 1451, 1286, 1053 cm^{-1}; ES HRMS *m/z* $(M+Na)^+$ calcd 325.0874, obsd 325.0874.

4.2.10. (+)-(*S*)-Ethyl (diphenylmethanesulfinyl)acetate (+)-(*S*)-7. The title compound was obtained in 87% yield from compound (−)-**6** following the same procedure as above. $[\alpha]_D^{22} = +56.2$ (*c* 1.0, $CHCl_3$).

Acknowledgements

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14. CCDC 245174 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.