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# On the mechanism of conversion of 4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)-isoquinolones to indeno[1,2-*c*]isoquinolines by thionyl chloride

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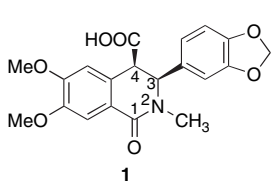
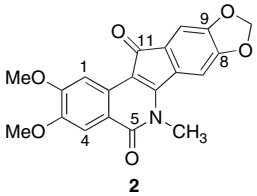
**Abstract**—It has been known for a long time that thionyl chloride can effectively mediate the transformation of 4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)-isoquinolones to indeno[1,2-*c*]isoquinolines. The mechanism of this unique transformation, however, remains to be established. Evidence is presented to demonstrate that (1) the two-electron dehydrogenation precedes Friedel–Crafts cyclization and (2) the two-electron dehydrogenation occurs via H-4 deprotonation and subsequent O-sulfinylation of the lactam moiety instead of C-sulfinylation of the carbon α to the carboxyl group.


## 1. Introduction

In 1978, the direct transformation of *cis* acid **1** to indeno-[1,2-*c*]isoquinoline **2** by thionyl chloride was reported.[1] Since the establishment of compound **2** as a novel non-camptothecin topoisomerase I inhibitor,[2] a number of analogs of **2** have been synthesized using this thionyl chloride-mediated oxidation/Friedel–Crafts cyclization methodology.[3–9] Despite its effectiveness in providing access to different substituted indenoisoquinolines, the exact mechanism of the thionyl chloride-mediated oxidation/Friedel–Crafts cyclization of **1** is still not established. Herein, detailed studies are described on the mechanism of this conversion employing differentially substituted substrate analogs to support a mechanism in which dehydrogenation precedes Friedel–Crafts cyclization and the lactam functionality plays an essential role in the dehydrogenation process.



**1**



**2**

*Keywords*: Thionyl chloride; Oxidation; Indenoisoquinoline; Intramolecular Friedel–Crafts reaction.
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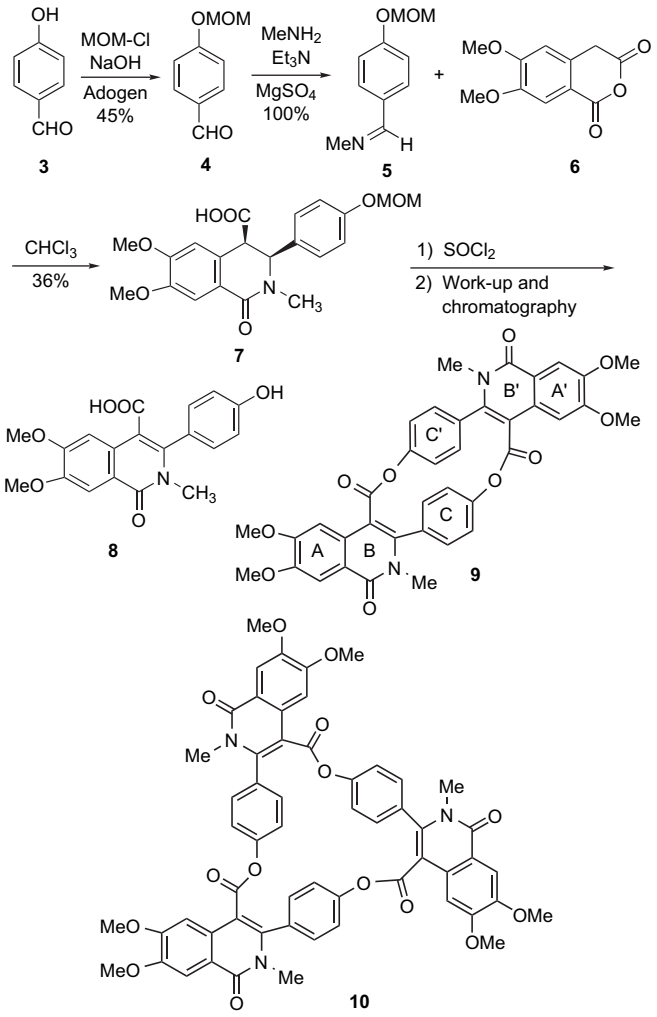
## 2. Results and discussion

To determine if $SOCl_2$-mediated oxidation can proceed without prior Friedel–Crafts acylation, *cis* acid **7** with a less-activated 3-phenyl ring than **1** was designed and synthesized (Scheme 1). Condensation of 3,4-dimethoxyhomophthalic anhydride (**6**)[1] with Schiff base **5**, prepared from MOM-protected aldehyde **4** and $MeNH_2$, yielded the *cis* acid **7**, whose relative stereochemistry was determined by the observed 6.2 Hz coupling constant for the two methine protons.[10] Treatment of the *cis* acid **7** with $SOCl_2$ gave three isolated compounds **8**, **9**, and **10** in 11, 31, and 28% yields, respectively. Therefore, it is clear that the $SOCl_2$-mediated dehydrogenation step can proceed without prior Friedel–Crafts cyclization. Previous studies indicated that the dehydrogenated intermediate derived from **1** could undergo Friedel–Crafts cyclization in the presence of thionyl chloride to afford **2**, but the Friedel–Crafts product derived from **1** did not undergo dehydrogenation to yield **2** with thionyl chloride.[1] These results, in combination with the present study, make it clear that dehydrogenation precedes the Friedel–Crafts acylation during the conversion of **1** to **2** by thionyl chloride. What remains to be determined is the mechanism of the dehydrogenation step.

Compounds **9** and **10** are novel macrocyclic systems containing 16-membered and 24-membered rings with either two or three benzene rings, respectively. Interestingly, the chemical shifts of the four protons in the substituted benzene




**Scheme 1**.

ring C of macrodilide **9** are different from each other[11] and one of the protons is significantly shifted upfield to 5.60 ppm. The C and C′ rings are equivalent so that the eight protons on the two rings appear as four doublets of doublets. In order to understand the unusual $^1$H NMR spectrum of this compound, the geometry was optimized at the AM1 theory level in Gaussian03.[12] It is reasonable to assume that the optimized AM1 structure (Fig. 1) would provide a valid model on which to base the interpretation of the $^1$H NMR data. Due to the differential shielding effect from the C′ ring, the two pairs of protons on the C ring are no longer identical, and vice versa. Furthermore, since the proton labeled 'a' in Figure 1 is located directly over the ring current from ring C′, it experiences an unusually strong shielding effect and thus appears more upfield in the $^1$H NMR spectrum. The

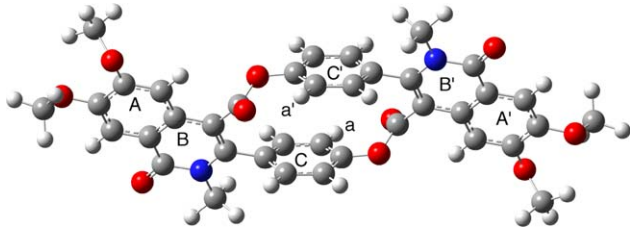
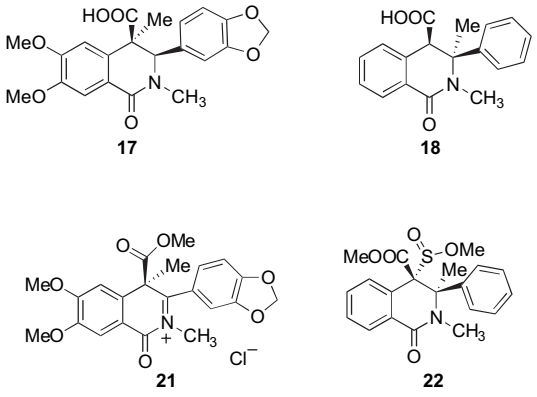


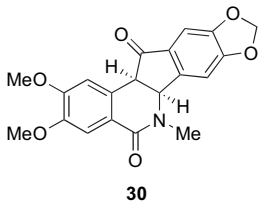

**Figure 1**. AM1 optimized geometry of compound **9**.

NMR results indicate that the conformational mobility of the macrodilide ring of **9** is limited by the π–π stacking interaction of the two aromatic rings, and this conclusion is also consistent with the AM1 calculation (Fig. 1). The predominant formation of this macrodilide in the reaction mixture is likely due to the effect of a combination of predisposed orientation of 3-phenyl and 4-carboxyl groups in **8**[13] and product stability rendered by the π–π stacking interaction of the C and C′ rings, which have an appropriate distance of 3.45 Å for stacking.[14]

Originally, we proposed the oxidation step involving Mechanism 1 as shown in Scheme 2 on the basis of the reported $SOCl_2$ dehydrogenation reactions of substrates lacking lactam functionality.[1] However, two alternative Mechanisms 2 and 3 involving participation of the lactam functionality are also intriguing,[15] especially because Mechanism 1 entails the formation of a quaternary carbon in a very sterically congested environment. In order to distinguish these mechanisms, two interrupting analogs **17**[16] and **18** were designed and synthesized. When **17** was treated with $SOCl_2$ at room temperature for 5 h, the typical time frame to convert *cis*-**1** to **2**,[1] followed by methanol work up, only ester **19**[16] was obtained quantitatively. However, prolonged reaction of **17** with $SOCl_2$ for 36 h resulted in the formation of 18% chlorinated compound **20** and 77% of ester **19** (Scheme 3). The failure to observe the formation of **21**, or a derivative of it, argues against Mechanism 2 (Scheme 2). Based on the relatively high p$K_a$ of H-3 compared to H-4, which is doubly activated by both carboxyl group and lactam, Mechanism 2 requiring deprotonation at H-3 in the presence of H-4 is also not favored.

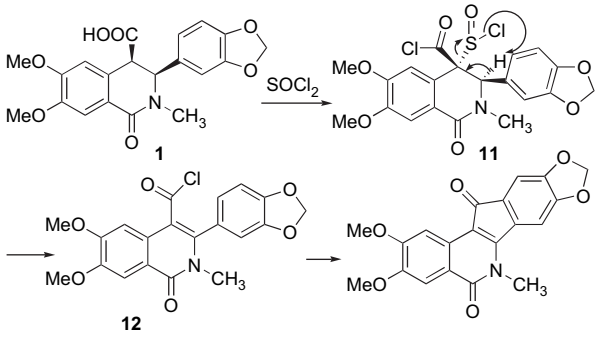



To avoid the complications resulting from the nucleophilic aromatic rings present in **17**, a simplified analog **18** was designed and synthesized (Scheme 4). Ketimine formation between acetophenone and methylamine in the presence of $TiCl_4$[17] afforded **24**, which was condensed with homophthalic anhydride (**25**) to give a pair of diastereomers **26** and **18** in 16 and 3% yields, respectively. The corresponding methyl esters were furnished by treating the individual acids with $TMSCHN_2$ in MeOH–benzene. The relative configurations of **18**, **26**, **27**, and **28** were determined primarily by the chemical shift differences of H-4, 3-Me, and 4-COOMe due to the shielding effect of the 3-phenyl ring and the electron-withdrawing effect of the 4-carbonyl (Table 1).[18,19] The structure of compound **28** was further confirmed by single crystal X-ray analysis (see Supplementary data).

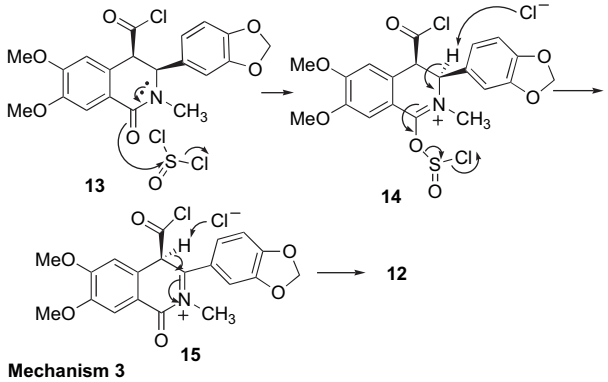


**30**

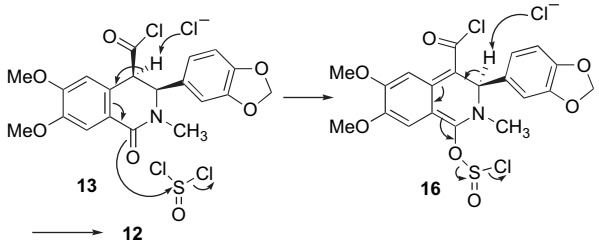
**Mechanism 1**



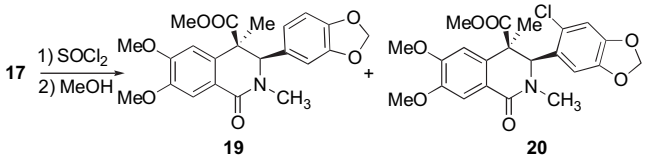
**Mechanism 2**



**Mechanism 3**

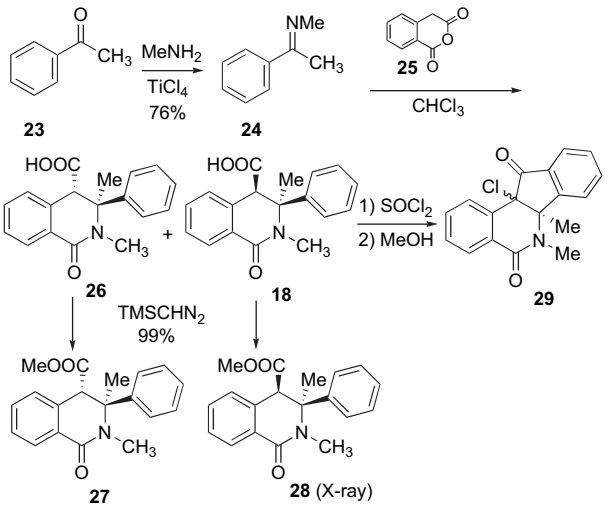


**Scheme 2**.



**Scheme 3**.

When acid **18** was treated with $SOCl_2$ at room temperature for 5 h, followed by methanol treatment, the only product formed was the ester **28**. On the other hand, when the reaction time of $SOCl_2$ treatment was prolonged to 36 h, a minor product **29** (5%) was also formed besides the ester **28** (92%). The formation of cyclized product **29** is very informative as it suggests that C-4 must become $sp^2$-hybridized before



**Scheme 4**.

**Table 1**. Chemical shift differences (ppm) between **18**, **26**, **27**, and **28**

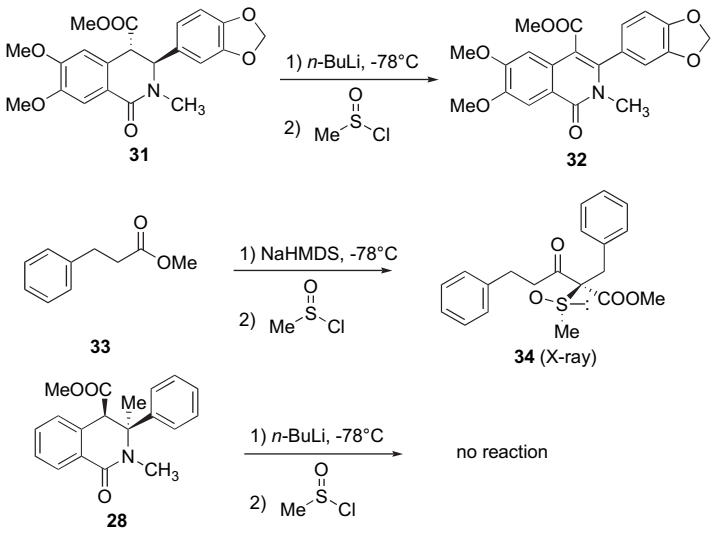
| Compound | H-4 | 3-Me | 4-COOMe |
|---|---|---|---|
| **18** | 3.82 | 1.66 | N/A |
| **26** | 4.12 | 1.86 | N/A |
| **27** | 4.18 | 1.81 | 3.62 |
| **28** | 3.75 | 1.58 | 3.14 |

cyclization instead of cyclizing from the original $sp^3$-hybridization state, which does not cyclize as evidenced by the failure to form any cyclized product derived from **17**, and failure to form **30** from **1** under similar treatment.[1] The failure to form even a trace of the sulfinate ester **22** and formation of **29** suggests that Mechanism 3 is the most likely one accounting for the oxidation step mediated by $SOCl_2$.

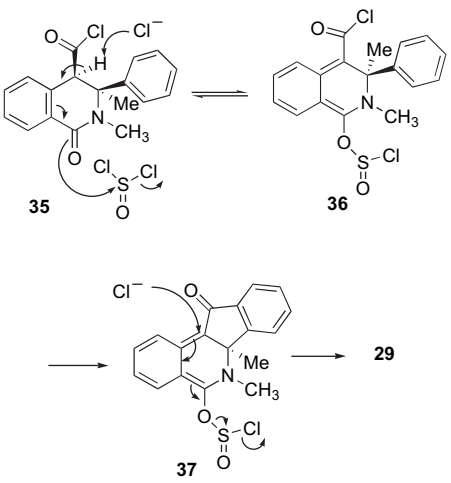
Further evidence to support Mechanism 3 comes from the reactions of methanesulfinyl chloride[20] with various esters (Scheme 5). Reaction of the enolate derived from ester **31** with methanesulfinyl chloride resulted in the formation of dehydrogenated product **32** in 75% yield. On the other hand, treatment of methyl 3-phenylpropionate (**33**) with NaHMDS followed by methanesulfinyl chloride gave methyl sulfoxide **34** diastereoselectively, whose structure was confirmed by single crystal X-ray analysis (see Supplementary data).

The formation of **34** is expected since elimination of sulfinic acid usually is slow[21,22] and requires high temperature compared to elimination of selenic acid.[23,24] If the oxidation reaction were to involve Mechanism 1, then similar treatment of ester **28** with methanesulfinyl chloride would generate the corresponding methyl sulfoxide. However, this treatment only resulted in the recovery of starting material. These observations indicate the mechanism shown in Scheme 6 for the formation of **29**. The acyl chloride **35** undergoes a reversible reaction with $SOCl_2$ to give *O*-sulfinilated species **36**, whose C-4 is in an $sp^2$ hybridization state, followed by cyclization to afford **37**. Chloride addition and elimination of sulfur monoxide from **37** provide the observed chloride **29**.

More direct evidence to support the participation of the amide functionality in the oxidation process is the

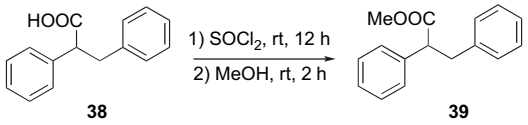



**Scheme 5**.




**Scheme 6**.

observation that treatment of 2,3-diphenyl-propionic acid (**38**) with $SOCl_2$, followed by MeOH, only resulted in the formation of the corresponding methyl ester **39** (Scheme 7). No oxidation product was observed in this case. The acid **38** is a simplified analog of **1** lacking the lactam functionality, and the inability of **38** to undergo the oxidation reaction indicates lactam participation in the oxidation of **1** by $SOCl_2$.




**Scheme 7**.

## 3. Conclusions

The transformation from *cis* acid **1** to indenoisoquinoline **2** by thionyl chloride involves a two-electron dehydrogenation followed by Friedel–Crafts cyclization. Although Mechanism 1 (Scheme 2) has been proposed for most of the oxidations mediated by thionyl chloride,[25–31] Mechanism 3 involving deprotonation at H-4 and subsequent O-sulfinylation of the amide is the most likely one accounting for the dehydrogenation of *cis* acid **1** based on the present experimental data presumably due to the sterics and the presence of an additional amide functionality.

## 4. Experimental

### 4.1. 4-Methoxymethoxybenzaldehyde (4)[32]

*Method A*: a solution of NaOH (1.3 g in 16 mL $H_2O$) was added to a stirred solution of 4-hydroxybenzaldehyde (2.0 g, 16.4 mmol) and Adogen® (1.3 g) in $CH_2Cl_2$ (50 mL). Then MOM-Cl (1.98 g, 24.5 mmol) was added. The resulting biphasic mixture was stirred at room temperature for 20 h. $CH_2Cl_2$ (100 mL) was added and the organic phase was separated and then washed successively with 1 N HCl (2×25 mL), $H_2O$ (2×25 mL), and brine (2×25 mL) and dried over $Na_2SO_4$. The solution was filtered and evaporated in vacuo and the resulting residue was subjected to flash column chromatography, eluting with *n*-hexane–ethyl acetate (10:1), furnishing **4** as a colorless oil (1.2 g, 45%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 9.87 (s, 1H), 7.80 (d, $J$=8.7 Hz, 2H), 7.11 (d, $J$=8.7 Hz, 2H), 5.22 (s, 2H), 3.46 (s, 3H); ESIMS $m/z$ (rel intensity) 167 ($MH^+$, 100). *Method B*: 4-hydroxybenzaldehyde (2.000 g, 16.37 mmol) was dissolved in dry DMF (50 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil) (0.786 g, 19.65 mmol) was carefully added and the reaction mixture was allowed to stir at 0 °C for 30 min. MOM-Cl (1.582 g, 19.65 mmol) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 1 h, then at room temperature for 1 h. The reaction was quenched with the addition of saturated aq $NH_4Cl$ (50 mL) and the solution was extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated aq $K_2CO_3$ (3×25 mL), saturated aq $NH_4Cl$ (3×25 mL), and brine (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography ($SiO_2$), eluting with a gradient of hexanes to 30% EtOAc/hexanes,

to provide a colorless oil (2.374 g, 87%) identical to the material furnished by Method A.

### 4.2. (4-Methoxymethoxy-benzylidene)methylamine (5)

Anhydrous $MgSO_4$ (1.8 g) and aldehyde **4** (817.5 mg, 4.92 mmol) were added sequentially to a stirred solution of $MeNH_2$ (2 M in methanol, 3.0 mL, 6.0 mmol) and $Et_3N$ (1 mL, 7.39 mmol) in $CHCl_3$ (10 mL). The resulting mixture was stirred at room temperature for 18 h. $CH_2Cl_2$ (50 mL) was added and the solution was washed with $H_2O$ (2×10 mL) and brine (2×10 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated in vacuo giving **5** as a colorless oil (882.8 mg, 100%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.19 (s, 1H), 7.62 (d, $J$=8.7 Hz, 2H), 7.03 (d, $J$=8.7 Hz, 2H), 5.18 (s, 2H), 3.46 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 161.7, 159.1, 130.2, 129.3 (2C), 116.1 (2C), 94.2, 56.1, 48.1; IR (KBr) 2938, 1652, 1607, 1510, 1237, 1153, 1081, 1003 cm$^{-1}$; ESIMS $m/z$ (rel intensity) 180 ($MH^+$, 100). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.37; H, 7.18; N, 7.59.

### 4.3. *cis*-4-Carboxy-6,7-dimethoxy-3-(4-methoxymethoxy-phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (7)

Anhydride **6** (269 mg, 1.2 mmol) was added in one portion to a stirred solution of imine **5** (217.2 mg, 1.2 mmol) in $CHCl_3$ (1.2 mL). The solution became clear and 3 h later a light yellow precipitate formed in the reaction mixture. The precipitate was collected and washed with $CHCl_3$ (1 mL) giving **7** as an off-white powder (173 mg, 36%): mp 218–220 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.51 (s, 1H), 7.11 (s, 1H), 6.96 (d, $J$=8.7 Hz, 2H), 6.87 (d, $J$=8.7 Hz, 2H), 5.12 (s, 2H), 5.01 (d, $J$=6.2 Hz, 1H), 4.59 (d, $J$=6.2 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.32 (s, 3H), 2.87 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 170.8, 163.0, 156.5, 151.2, 147.7, 130.1, 128.9 (2C), 127.2, 121.5, 115.8 (2C), 110.8, 109.8, 93.6, 62.6, 55.6, 55.5 (2C), 47.5, 33.4; ESIMS $m/z$ (rel intensity) 402 ($MH^+$, 100); IR (film) 2939, 1739, 1596, 1511, 1489, 1287, 1230, 1147, 1079, 754, 624 cm$^{-1}$. Anal. Calcd for $C_{21}H_{23}NO_7 \cdot H_2O$: C, 60.14; H, 6.01; N, 3.34. Found: C, 60.45; H, 5.64; N, 3.36.

### 4.4. 4-Carboxy-1,2-dihydro-3-(4-hydroxyphenyl)-6,7-dimethoxy-2-methyl-1-oxo-isoquinoline (8), dilide (9) and trilide (10)

Acid **7** (39.5 mg, 0.098 mmol) was treated with thionyl chloride (0.4 mL) at room temperature for 4 h. Then excess thionyl chloride was evaporated in vacuo and benzene (3×3 mL) was added and evaporated in vacuo. The residue was subjected to flash column chromatography, eluting with $CHCl_3$–MeOH (100:0–4:1), to provide a white powder **8** (4 mg) and a mixture of **9** and **10**. The mixture of **9** and **10** was further purified by preparative TLC on silica gel [$CHCl_3$–MeOH (50:1)] giving **9** (10 mg) and **10** (9 mg) as white powders. Product **8**: mp>254 °C (dec). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.90 (br s, 1H), 7.87 (s, 1H), 7.40 (d, $J$=8.4 Hz, 2H), 7.05 (s, 1H), 6.86 (d, $J$=8.4 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.18 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.2, 160.6, 158.0, 153.2, 148.9, 141.1, 130.6 (2C), 128.3, 124.8, 117.8, 115.2 (2C), 112.9, 107.3, 104.3, 55.6 (2C), 33.5; IR (KBr) 3489, 3441, 3137, 2956, 1685, 1609, 1512, 1274, 1225, 1176 cm$^{-1}$; ESIMS $m/z$ (rel intensity) 356 ($MH^+$, 100). Anal. Calcd for $C_{19}H_{17}NO_6 \cdot 1.5H_2O$: C, 59.68; H, 5.27; N, 3.66. Found: C, 59.93; H, 5.05; N, 3.51. Product **9**: mp 383–385 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (s, 2H), 7.60 (dd, $J$=8.4, 2.4 Hz, 2H), 7.45 (dd, $J$=8.4, 2.4 Hz, 2 H), 7.29 (dd, $J$=8.1, 2.1 Hz, 2H), 7.23 (s, 2H), 5.60 (dd, $J$=8.1, 2.1 Hz, 2H), 4.02 (s, 6H), 4.00 (s, 6H), 3.35 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.9 (2C), 161.7 (2C), 154.1 (2C), 150.8 (2C), 149.9 (2C), 142.6 (2C), 133.2 (2C), 131.0 (2C), 130.4 (2C), 128.3 (2C), 123.8 (2C), 122.7 (2C), 118.8 (2C), 110.7 (2C), 108.2 (2C), 103.7 (2C), 56.3 (2C), 34.2 (2C), 29.7 (2C); ESIMS $m/z$ (rel intensity) 1349 (2M+$H^+$, 53), 675 ($MH^+$, 100); IR (film) 2963, 2905, 1732, 1651, 1609, 1502, 1415, 1260, 1094, 1019, 799, 703 cm$^{-1}$. Anal. Calcd for $C_{38}H_{30}N_2O_{10}$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.34; H, 4.46; N, 3.98. Product **10**: mp 402–404 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.87 (s, 3H), 7.58 (s, 3H), 7.36 (d, $J$=9.0 Hz, 6H), 7.04 (d, $J$=9.0 Hz, 6H), 4.03 (s, 9H), 3.95 (s, 9H), 3.31 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.5 (3C), 162.2 (3C), 157.4 (3C), 154.0 (3C), 149.7 (3C), 142.5 (3C), 130.7 (6C), 129.0 (3C), 126.3 (3C), 118.5 (3C), 116.0 (6C), 112.5 (3C), 107.9 (3C), 104.2 (3C), 56.3 (6C), 34.5 (3C); ESIMS $m/z$ (rel intensity) 1012 ($MH^+$, 100); IR (film) 2921, 2851, 1722, 1647, 1610, 1501, 1422, 1312, 1267, 1200, 1147, 1053, 1023 cm$^{-1}$. Anal. Calcd for $C_{57}H_{45}N_3O_{15}$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.46; H, 4.32; N, 3.96.

### 4.5. *cis*-3-(2-Chloro-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methoxycarbonyl-2,4-dimethyl-1-oxo-isoquinoline (20)

$SOCl_2$ (1 mL) was added to a stirred solution of acid **17** (10 mg, 0.025 mmol) at room temperature. The resulting mixture was stirred at room temperature for 36 h and then the excess $SOCl_2$ was evaporated under reduced pressure. The resulting residue was treated with MeOH (5 mL) and the reaction mixture was heated under reflux for 2 h. Methanol was evaporated and the residue was separated by preparative TLC, developing with $CHCl_3$–MeOH (100:1), yielding compound **20** (2 mg, 18%) and ester **19** (8 mg, 77%). Compound **20** was isolated as a viscous oil that became a white solid upon standing: mp 145–146 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (s, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 6.41 (s, 1H), 5.88 (d, $J$=1.2 Hz, 1H), 5.86 (d, $J$=1.2 Hz, 1H), 5.18 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.51 (s, 3H), 3.00 (s, 3H), 1.78 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.8, 162.7, 152.2, 148.3, 148.2, 147.1, 132.9, 128.4, 125.6, 120.2, 110.4, 109.9, 109.2, 107.7, 102.0, 65.5, 56.1, 52.2, 34.1, 29.7; IR (film) 3451, 2925, 2854, 1736, 1651, 1602, 1508, 1479, 1283, 1237, 1120, 1038, 928, 782 cm$^{-1}$; ESIMS $m/z$ (rel intensity) 450 ($^{37}$Cl−$MH^+$, 34), 448 ($^{35}$Cl−$MH^+$, 100); HRESIMS $m/z$ calcd for 448.1163, found 448.1161.

### 4.6. Phenylethylidene-*N*-methylamine (24)[33]

$MeNH_2$ (2.0 M in THF, 15 mL, 30 mmol) was added to a stirred solution of acetophenone (**23**) (1.2 g, 10 mmol) in toluene (10 mL) at −10 °C. A solution of $TiCl_4$ (0.55 mL,

5 mmol) in toluene (2 mL) was then added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature and then heated at 90 °C for 2 h. After cooling to room temperature, the reaction mixture was allowed to stand overnight, filtered, and washed with toluene (100 mL). Evaporation of toluene yielded **24** as a blood-red oil (1.0 g, 76%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.71–7.76 (m, 2H), 7.33–7.40 (m, 3H), 3.34 (s, 3H), 2.23 (s, 3H); IR (film) 3057, 2961, 1635, 1445, 1285, 1026, 761, 694; EIMS *m*/*z* (rel intensity) 133 ($MH^+$, 8), 118 (100), 91 (33), 77 (88), 51 (62).

### 4.7. *cis*-4-Carboxy-1,2,3,4-tetrahydro-2,3-dimethyl-3-phenyl-1-oxo-isoquinoline (18) and *trans*-4-carboxy-1,2,3,4-tetrahydro-2,3-dimethyl-3-phenyl-1-oxo-isoquinoline (26)

Homophthalic anhydride (**25**) (520 mg, 3.2 mmol) was added to a stirred solution of ketimine **24** (427 mg, 3.2 mmol) in $CHCl_3$ (4 mL) at room temperature. The mixture was heated at reflux for 5 h. $CHCl_3$ was evaporated and the residue was subjected to flash column chromatography, eluting with $CHCl_3$ and $CHCl_3$–MeOH (10:1), yielding acid **18** (150 mg, 16%) and acid **26** (30 mg, 3%). Product **18**: a white solid, mp>200 °C (dec). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J$=6.6 Hz, 1H), 7.35–7.45 (m, 4H), 7.07–7.22 (m, 4H), 3.82 (s, 1H), 2.83 (s, 3H), 1.66 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 174.2, 165.9, 140.0, 133.0, 132.1, 128.9, 128.6, 128.5, 128.4 (2C), 128.0, 127.2, 127.0 (2C), 64.9, 58.3, 32.4, 24.0; IR (film) 2983, 1727, 1622, 1575, 1385, 1165, 1028, 760, 703; ESIMS *m*/*z* (rel intensity) 296 ($MH^+$, 100); HRESIMS *m*/*z* calcd for 296.1287, found 296.1281. Product **26**: a white solid, mp>186 °C (dec). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$=6.6 Hz, 1H), 7.08–7.30 (m, 7H), 6.98–7.00 (m, 1H), 4.12 (s, 1H), 3.10 (s, 3H), 1.86 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.4, 165.8, 142.7, 132.6, 132.0, 129.2, 128.8 (2C), 128.5 (2C), 127.5, 127.0, 125.3 (2C), 63.0, 57.1, 29.3, 25.4; IR (film) 3406, 2983, 1723, 1626, 1575, 1381, 1218, 1029, 762, 700; ESIMS *m*/*z* (rel intensity) 296 ($MH^+$, 100); HRESIMS *m*/*z* calcd for 296.1287, found 296.1287.

### 4.8. *trans*-1,2,3,4-Tetrahydro-4-methoxycarbonyl-2,3-dimethyl-1-oxo-3-phenylisoquinoline (27) and *cis*-1,2,3,4-tetrahydro-4-methoxycarbonyl-2,3-dimethyl-1-oxo-3-phenylisoquinoline (28)

$TMSCHN_2$ (2.0 M in hexane, 25 μL, 0.044 mmol) was added to a stirred suspension of acid **18** or **26** (10 mg, 0.033 mmol) in MeOH–benzene (1:3.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min and the solution became clear. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography, eluting with $CHCl_3$–MeOH (20:1), yielding a white solid (10 mg, 99%). Product **28**: a chunk crystal (from *n*-hexane–EtOAc), mp 174–175 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10 (dd, $J$=6.0, 3.3 Hz, 1H), 7.17–7.34 (m, 7H), 7.00 (dd, $J$=6.0, 3.3 Hz, 1H), 3.75 (s, 1H), 3.14 (s, 3H), 2.77 (s, 3H), 1.58 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.3, 165.6, 140.7, 133.1, 132.0, 128.8, 128.7, 128.5 (3C), 128.0, 127.1, 126.8 (2C), 65.1, 58.5, 52.0, 32.3, 23.9; ESIMS *m*/*z* (rel intensity) 310 ($MH^+$, 100). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 74.02; H, 6.36; N, 4.39. Summary of X-ray crystal data: $C_{19}H_{11}NO_3$; FW=309.37; $a$=11.4459(3) Å; $b$=7.8559(2) Å; $c$=18.1780(5) Å; $\beta$=104.6058(17)°; vol=1581.70(7) Å$^3$; monoclinic; space group $P21/n$; $Z$=4; crystal size=0.41×0.39×0.35 mm; GOF=1.071; $R(F_o)$=0.039, $Rw(F_o^2)$=0.107. Product **27**: a white solid, mp 153–154 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10 (td, $J$=6.3, 1.2 Hz, 1H), 7.12–7.33 (m, 7H), 6.95 (dd, $J$=6.9, 1.8 Hz, 1H), 4.18 (s, 1H), 3.62 (s, 3H), 3.12 (s, 3H), 1.81 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.6, 165.5, 142.9, 132.8, 131.8, 129.2, 128.7 (2C), 128.5, 128.3, 127.5, 126.7, 125.4 (2C), 63.3, 57.4, 52.4, 30.4, 24.8; ESIMS *m*/*z* (rel intensity) 310 ($MH^+$, 100); HRESIMS *m*/*z* calcd for 310.1443, found 310.1444.

### 4.9. 12-Chloro-5,6,12,13-tetrahydro-6,13-dimethyl-5,11-dioxo-11*H*-indeno[1,2-*c*]isoquinoline (29)

The acid **18** (90 mg, 0.3 mmol) was treated with $SOCl_2$ (2 mL) at room temperature for 36 h. Then the excess $SOCl_2$ was evaporated to afford a residue, which was immediately dissolved in anhydrous MeOH (2 mL). The mixture was stirred at room temperature for 2 h. MeOH was removed in vacuo and the residue was subjected to flash column chromatography, eluting with *n*-hexane–EtOAc (3:1), yielding ester **28** (87 mg, 92%) and **29** (5 mg, 5%). Product **29**: a white solid, mp 158–160 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.11 (d, $J$=7.8 Hz, 1H), 7.76 (d, $J$=7.8 Hz, 1H), 7.67 (t, $J$=7.5 Hz, 2H), 7.59 (t, $J$=7.5 Hz, 1H), 7.52 (td, $J$=7.5, 1.5 Hz, 1H), 7.44 (t, $J$=7.5 Hz, 1H), 7.41 (td, $J$=7.5, 1.5 Hz, 1H), 3.39 (s, 3H), 1.83 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 163.5, 159.1, 142.9, 135.9 (2C), 133.7, 132.8, 131.8, 129.8, 129.6, 128.9, 128.1, 125.1, 123.8, 76.8, 67.1, 30.4, 26.8; ESIMS *m*/*z* (rel intensity) 312 ($^{35}ClMH^+$, 100), 314 ($^{37}ClMH^+$, 31); HRESIMS *m*/*z* calcd for $C_{18}H_{14}{}^{35}ClNO_2$ 311.0713, found 311.0720.

### 4.10. 6,7-Dimethoxy-4-methoxycarboxy-*N*-methyl-3-(3′,4′-methylenedioxyphenyl)-1(2*H*)-isoquinolone (32)

*n*-BuLi (0.16 mL, 2.5 M in hexane, 0.39 mmol) was slowly added to a stirred solution of ester **31** (129 mg, 0.32 mmol) in THF (2 mL) at −78 °C. The resulting solution was then stirred at −78 °C for 15 min and then a solution of methanesulfinyl chloride (32 mg, 0.32 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by slow addition of a saturated solution of $NH_4Cl$ (5 mL) and the product was extracted with $CHCl_3$ (3×20 mL). The combined organic layers were washed with $H_2O$ (2×5 mL) and brine (2×5 mL). The organic solution was dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography, eluting with $CHCl_3$, yielding **32** as a light yellow solid (92 mg, 72%), which displayed identical physical data with an authentic sample of **32** obtained differently.[15]

### 4.11. (±)-Methyl 2(*R*)-benzyl-2-(*S*)-methanesulfinyl-3-oxo-5-phenylpentanoate (34)

NaHMDS (3.04 mL, 1.0 M in THF, 3.04 mmol) was slowly added to a stirred solution of ester **33** (415 mg, 2.53 mmol) in THF (5 mL) at −78 °C. The resulting solution was then stirred at −78 °C for 30 min when methanesulfinyl chloride

(299 mg, 3.04 mmol) was added. The reaction mixture was then stirred at −78 °C for 1 h. The reaction was quenched by slow addition of $H_2O$ (5 mL) and the product was extracted with EtOAc (3×30 mL). The combined organic layers were washed with $H_2O$ (2×10 mL) and brine (2×10 mL). The organic solution was dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography, eluting with *n*-hexane–EtOAc (4:1), yielding a white solid **34** as colorless needles (320 mg, 71%): mp 119–120 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.20–7.36 (m, 10H), 3.83 (d, $J$=13.8 Hz, 1H), 3.71 (s, 1H), 3.46 (d, $J$=13.8 Hz, 1H), 3.08–3.21 (m, 2H), 2.95–3.03 (m, 2H), 2.41 (s, 3H). Summary of X-ray crystal data: $C_{20}H_{22}O_4S$; FW=358.46; $a$=24.0662(7) Å; $b$=6.2232(2) Å; $c$=26.5189(9) Å; $\beta$=111.6340(15)°; vol=3691.9(2) Å$^3$; monoclinic; space group $P121/n1$; $Z$=8; crystal size=0.50×0.31×0.13 mm; GOF=1.018; $R(F_o)$=0.039, $Rw(F_o^2)$=0.088. Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.19; S, 8.95. Found: C, 66.74; H, 6.02; O, 8.66.

### 4.12. Methyl 2,3-diphenyl-propanoate (39)[33]

Thionyl chloride (1 mL) was added to acid **38** (116 mg, 0.5 mmol) at room temperature. The mixture was stirred at room temperature for 12 h. Excess thionyl chloride was removed under reduced pressure. The residue was treated with methanol (2 mL) and stirred at room temperature for 2 h. Methanol was removed under reduced pressure giving a colorless oil (120 mg, 100%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.99–7.20 (m, 10H), 3.75 (dd, $J$=9.0, 6.9 Hz, 1H), 3.45 (s, 3H), 3.31 (dd, $J$=13.8, 8.7 Hz, 1H), 2.91 (dd, $J$=13.8, 6.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.6, 138.9, 138.5, 128.8 (2C), 128.5 (2C), 128.2 (2C), 127.8 (2C), 127.3, 126.2, 53.5, 51.8, 39.7.

### 4.13. X-ray crystallographic data for 28 and 34

Crystallographic data (excluding structure factors) for the compounds **28** and **34** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 601047 and 601048, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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## Supplementary data

ORTEP drawings and crystallographic information files of compounds **28** and **34**. $^1$H NMR spectra of compounds **9**, **10**, **20**, **27**–**29**, and **39**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.072.

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