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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 1395–1401

Unexpected regiospecific reactivity of a substituted phthalic anhydride

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Received 12 September 2006; revised 10 November 2006; accepted 30 November 2006
Available online 19 December 2006

Abstract—Regioselective nucleophilic addition at C1 of anhydride **7** by a range of nucleophiles occurs to produce amide, ester and thioester derivatives **8–15** (60–99%). The increased electrophilic reactivity of the C1 carbonyl group of anhydride **7** is supported by a competition experiment with phthalic anhydride. Unexpected formation of lactams **18** and **19** from amides **12** and **13** was shown to proceed via the lactamols **16** and **17** and could be controlled by the reaction conditions. The solid-state structure of **19** is reported.

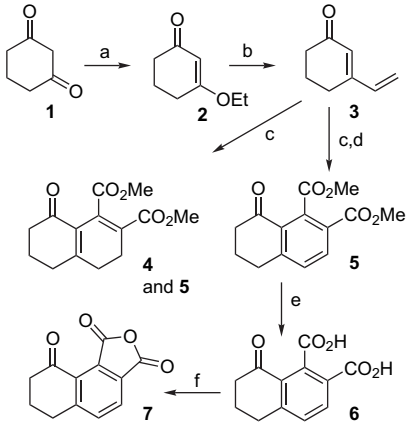
1. Introduction

Phthalic anhydrides react with a range of nucleophiles, such as alcohols,[1–4] Grignard reagents,[5,6] sugars[7–9] and thienyllithium[10] to produce the carboxylic acid derivative arising from anhydride opening. With hydroxylamine[11] and other amines[12] they provide phthalimides, which can be used in the synthesis of pharmaceutically interesting molecules,[13–18] natural products,[19,20] compounds that are chromophores,[21] and compounds that have chiroptical,[22] fluorescent[23] or electron transfer properties.[24,25] They are also useful as polymer-supported reagents.[26–28] There are very few phthalic anhydrides with a gamma aliphatic ketone, and reactions are restricted to ring opening of the anhydride via Friedel–Crafts acylation[29] or with an alcohol to form an ester carboxylic acid.[30–31] Herein, we report the unexpected regiospecific ring opening of a phthalic anhydride with a gamma aliphatic ketone, compound **7**.

2. Results and discussion

Naphthofurantrione **7**, a useful building block for the synthesis of analogues of the natural product hyphodermin B,[32] was prepared from cyclohexan-1,3-dione **1**. Reaction of **1** with ethanol in the presence of hydrochloric acid gave ketoenol **2**. 1,4-Addition of vinyl magnesium bromide to **2** in ether followed by a dilute acid quench gave ketodiene **3**. As ketodiene **3** decomposed upon standing, it was submitted to a rapid plug column upon work-up and then used immediately in the next step. Diels–Alder cycloaddition of acetylene dicarboxylate in the presence of hydroquinone gave, after work-up, a mixture of the diesters **4** and **5**. The diester **5** was the exclusive product following a dehydrogenation step using palladium on charcoal in acetic acid.

Alkaline hydrolysis of diester **5**, followed by acidification gave diacid **6**, which was converted to anhydride **7** by heating at 50–60 °C with acetic anhydride. In summary, anhydride **7** was obtained in five steps and 27% overall yield from cyclohexan-1,3-dione **1** (Scheme 1).



Scheme 1. Synthetic route for the preparation of anhydride **7**. Reagents and conditions: (a) ethanol, HCl, rt, 16 h, 96%; (b) vinyl magnesium bromide, ether, rt, 16 h, 75%; (c) 1.5% hydroquinone, dimethyl acetylene dicarboxylate, toluene, reflux, 48 h; (d) Pd/C, acetic acid, reflux, 16 h, 41%; (e) 10% NaOH, THF, rt, 4 h, 65%; (f) acetic anhydride, 50 °C, 16 h, 98%.

Keywords: (3–8) Phthalic anhydride; Nucleophilic addition; Intramolecular ring closure; Hydrobenzoindole.
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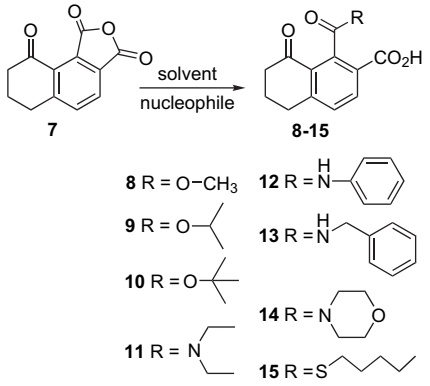
0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.11.090

When anhydride **7** was treated with a range of nucleophiles, the derivatives **8–15** were obtained (Scheme 2). In each case, nucleophilic attack occurred exclusively at C1 of the anhydride. Reactions with alcohols (methanol, isopropanol and *tert*-butanol—Table 1, entries 1–4) were performed in the presence of pyridine (1–5 equiv, Table 1, entries 1–4). In the absence of pyridine, which can act as a nucleophilic and/or base catalyst, the reaction was slow. Good yields of esters **8** and **9** were obtained, except in the case of *tert*-butanol, which gave the diacid **6**, presumably via competitive hydrolysis of **7** with adventitious water.



Scheme 2. Synthetic route for the preparation of derivatives **8–15**.

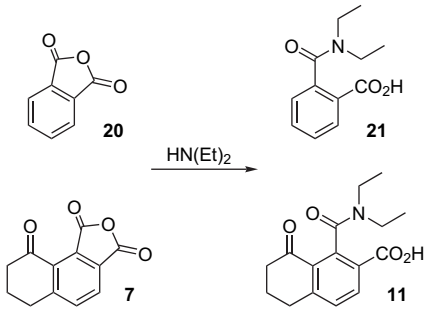
As expected, reactions with amines (benzylamine, aniline, diethylamine and morpholine) were much faster and did not require the presence of pyridine (Table 1, entries 5–9). However, a polar solvent was required to fully dissolve the starting anhydride **7**. The slightly slower reaction in the case of secondary amines (diethylamine, morpholine) was attributed to steric factors. In these reactions, a minor precipitate was observed when complete formation of the product had occurred. The precipitate was attributed to diacid **6** arising from the presence of traces of water. Although aniline and benzylamine gave near quantitative yields of **12** and **13**, respectively, isolation of these products by column chromatography was complicated by the formation of the corresponding ring closed products **16** and **17**.

1-Pentanethiol (Table 1, entry 10) reacted with anhydride **7** in the presence of pyridine in an analogous manner to give the thiol ester **15**.

Table 2. Product ratios from reaction of **7** and **20** with triethylamine

Entry	Reactants (ratio)			Products (ratio in %)			
	7	**20**	Et_2NH	**7**	**11**	**20**	**21**
1	1	1	2	0	47	0	53
2	2	2	1	26	24	45	5
3	10	10	1	40	8	51	1

The remarkable regioselectivity observed in the ring opening of anhydride **7** suggested that the C1 carbonyl was very electrophilic. This result was consistent with a modelling study carried out previously within our group on a similar compound.[32] To examine whether the gamma-ketone had an inductive (activating) influence on the anhydride **7**, a competitive reaction was carried out by treating a mixture of phthalic anhydride **20** and the gamma keto anhydride **7** with diethylamine. Initially, a 1:1 mixture of **7** and **20** was treated with 2 equiv of diethylamine. As expected, this resulted in a ~1:1 ratio of **11** and **21** (Table 2, entry 1, Scheme 3). By contrast when anhydrides **7** and **20** were present in excess relative to the diethylamine (Table 2, entries 2 and 3), **11** was formed as the major product with only minor amounts of **21** being observed. This confirmed the activated nature of the C1 carbonyl group in anhydride **7**.



Scheme 3. Reaction of **7** and **20** with diethylamine.

During the synthesis of benzylamide **13**, when anhydride **7** was treated with benzylamine in ethyl acetate for 1 h, unexpected formation of lactamol **17** occurred in 72% yield. The structure of **17** was unambiguously assigned using gCOSY, gHSQC and gHMBC NMR spectroscopy, with a diagnostic correlation between the CH_2 at δ 4.93 ppm and C8a at δ 87.0 ppm being observed in the gHMBC. The spectral data

Table 1. Derivatives of anhydride **7** shown in Scheme 2

Entry	Nucleophile	Solvent	Reaction conditions	Product	Yield (%)
1	Methanol	Pyridine[a] in methanol	rt, 16 h, N_2	**8**	64
2	Isopropanol	Pyridine[a] in isopropanol	rt, 16 h, N_2	**9**	94[b]
3	Isopropanol	Pyridine[c] in isopropanol	rt, 16 h, N_2	**9**	60
4	*tert*-Butanol	Pyridine[a] in *tert*-butanol	rt, 16 h, N_2	**6**	99[d]
5	Benzylamine[c]	$CHCl_3$[e]	rt, 45 min, N_2	**13**	97[b]
6	Aniline[c]	$CHCl_3$[e]	rt, 15 min, N_2	**12**	99[b]
7	Diethylamine[c]	Ethyl acetate	rt, 2 h, N_2	**11**	69
8	Diethylamine[c]	Ethyl acetate	rt, 16 h, N_2	**11**	80
9	Morpholine[c]	Ethyl acetate	rt, 3 h, N_2	**14**	82
10	1-Pentanethiol[a]	Pyridine[a] in dichloromethane	rt, 16 h, N_2	**15**	60

[a] 5.0 equiv.
[b] Crude yield, >98% pure.
[c] 1.0 equiv.
[d] NMR yield, >95% pure.
[e] Chloroform was de-acidified by passing through K_2CO_3 prior to use.

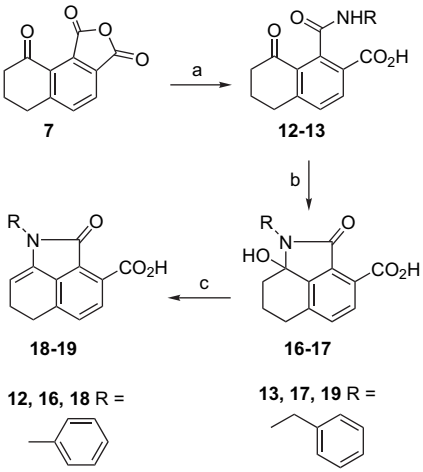
for **17** were acquired in DMSO-d_6. By contrast, it was noted that upon standing for 3 h in $CDCl_3$, **17** underwent total conversion to lactam **19**. A triplet at δ 5.96 ppm in the ^{1}H NMR spectrum of **19** was diagnostic for formation of **19**. In the course of this work, **19** crystallised from toluene as pale yellow plates suitable for single crystal X-ray structure determination. In the structure of **19**, formation of a strong intramolecular O–H···O hydrogen bond between the carboxy hydroxyl group and the C2 carbonyl oxygen results in the co-planarity of the carboxylic acid group and the 'lactam' ring system (Fig. 1).

Next, we sought to establish reaction conditions for the controlled formation of **13**, **17** and **19**. We considered that the carboxylic acid group in the product or solvent may have catalysed the formation of **17** from **7** via **13**, and residual acid in $CDCl_3$ may have catalysed the dehydration of **17** to **19**.

Chloroform was de-acidified by passing it through a plug of potassium carbonate. Treatment of anhydride **7** with benzylamine in de-acidified chloroform for 45 min gave amide **13**. When a longer reaction time of 2 h was used, a mixture of **13** and **17** in a 89:11 ratio was obtained.

Stirring amide **13** in de-acidified ethyl acetate for 48 h directly gave lactamol **17**. Dissociation of the carboxylic acid proton of **13** will be influenced by the solvent.[33] Formation of lactamol is presumably via activation of the ketone group through protonation and subsequent attack by the amide nitrogen. Lactamol **17** was surprisingly stable, provided it was kept in the solid state. However, it was easily dehydrated to lactam **19** by treatment with two drops of hydrochloric acid in chloroform.

When aniline was reacted with anhydride **7**, a similar reactivity of the gamma-ketone in **7** was observed. Amide **12** was obtained from anhydride **7** in de-acidified chloroform after 15 min. A longer reaction time (45 min) resulted in a mixture of amide **12** and lactamol **16** (84:16, respectively). Amide **12** underwent ring closure in acetone (or ethyl acetate) after 48 h to give lactamol **16**. Recrystallisation of **16** from de-acidified ethyl acetate or acetone resulted in the formation of a minor amount of lactam **18**. Lactamol **16** was easily dehydrated to lactam **18** by treatment with one drop of hydrochloric acid in chloroform (Scheme 4). The apparent increased reactivity of aniline compared to benzylamine towards the anhydride **7** can be attributed to the higher basicity of benzylamine and its consequent protonation by the carboxylic acid moiety in the products.



Scheme 4. Synthetic route for the preparation of **18** and **19**. Reagents and conditions: (a) benzylamine, chloroform (de-acidified), rt, 45 min, **13** 97%; aniline, chloroform (de-acidified), rt, 15 min, **12** 99%. (b) Ethyl acetate (de-acidified), rt, 48 h, **17** 99%; acetone, rt, 48 h, **16** 96%. (c) Two drops HCl, chloroform, rt, 4 h, **19** 72%; one drop HCl, chloroform, rt, 16 h, **18** 78%.

In conclusion, the regioselective nucleophilic addition at C1 of anhydride **7** by a range of nucleophiles, to obtain amide, ester and thioester derivatives **8–15** is reported. The increased electrophilic reactivity of the C1 carbonyl group of anhydride **7** is supported by a competition experiment with phthalic anhydride. Unexpected formation of lactams **18** and **19** from amides **12** and **13** was observed. The solid-state structure of **19** is reported. The unexpected formation of lactams **18** and **19** was shown to proceed via the lactamols **16** and **17** and could be controlled by the reaction conditions. This potentially provides facile access to such tricyclic systems present in bioactive natural products, such as piperolactams[34] and aristololactams.[35]

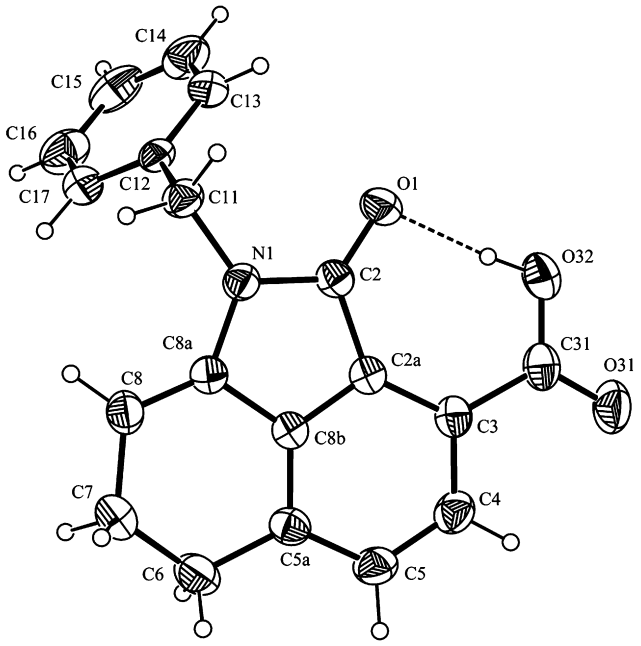


Figure 1. ORTEP-3 drawing of lactam **19** (30% ellipsoidal probability).

3. Experimental

3.1. General procedure

See Supplementary data.

3.1.1. 8-Oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylic acid (6). Sodium hydroxide (10% aqueous solution, 35 mL) was added to diester **5**[36] (1.74 g, 6.65 mmol) in tetrahydrofuran (15 mL), and the mixture stirred at room temperature for 4 h. Tetrahydrofuran was removed under

reduced pressure, and the aqueous layer was washed with hexane (100 mL) and ethyl acetate (100 mL). The aqueous layer was acidified (pH 1) by the addition of concentrated hydrochloric acid, and extracted with ethyl acetate (4×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to afford a pale yellow solid. Recrystallisation (ethyl acetate) of the solid gave compound **6** as an amorphous white solid (1.01 g, 65%). Mp 222–223 °C. IR (KBr) cm^{-1}: 1692. δ_H (400 MHz, DMSO-d_6): 2.03 (2H, tt, *J* 6.2, 12.4 Hz, H6), 2.63 (2H, t, *J* 6.4 Hz, H7), 3.02 (2H, t, *J* 5.8 Hz, H5), 7.49 (1H, d, *J* 8.4 Hz, H4), 8.00 (1H, d, *J* 8.0 Hz, H3), 12.95 (2H, br s, CO_2H). δ_C (100 MHz, DMSO-d_6): 22.1 (C6), 29.6 (C5), 39.6 (C7), 127.5 (C2), 129.2 (C8a), 129.5 (C4), 133.8 (C3), 136.4 (C1), 149.4 (C4a), 166.3 (CO_2H), 169.2 (CO_2H), 196.3 (C8). MS (ESI) *m/z*: 257 ([M+Na]$^+$, 100%). Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.44; H, 4.47.

3.1.2. 7,8-Dihydro-*6H*-naphtho[1,2-*c*]furan-1,3,9-trione (7). Dicarboxylic acid **6** (866 mg, 3.70 mmol) was suspended in acetic anhydride (30 mL), and the mixture heated under nitrogen at 50 °C for 16 h. Co-evaporation of the solvent with toluene under reduced pressure gave compound **7** as an amorphous white solid (785 mg, 98%). Mp 185 °C. IR (KBr) cm^{-1}: 1845, 1774, 1698. δ_H (200 MHz, $CDCl_3$,): 2.25 (2H, tt, *J* 6.5, 13 Hz, H7), 2.84 (2H, t, *J* 6.7 Hz, H8), 3.15 (2H, t, *J* 6.1 Hz, H6), 7.81 (1H, d, *J* 7.8 Hz, H5), 8.06 (1H, d, *J* 7.6 Hz, H4). δ_C (100 MHz, $CDCl_3$): 22.6 (C7), 30.8 (C6), 39.5 (C8), 128.1 (C4), 130.1 (C9b), 132.3 (C3a), 133.3 (C9a), 137.2 (C5), 153.9 (C5a), 159.2 (C1), 162.5 (C3), 194.3 (C9). MS (ESI) *m/z*: 239 ([M+Na]$^+$, 100%), 223 ([M+Li]$^+$, 100%). EIMS *m/e*: 216 (M, 18%), 188 (M−CO, 40%), 172 (M−CO_2, 10%). HRMS calcd for $C_{12}H_8O_4$ [M]$^+$: 216.0423. Found: 216.0418.

3.1.3. 1-(Methoxycarbonyl)-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (8). Pyridine (353 μL, 4.15 mmol) was added to a suspension of anhydride **7** (180 mg, 0.83 mmol) in methanol (20 mL), and the mixture stirred under nitrogen at room temperature for 16 h. The solvent was removed under reduced pressure and aqueous hydrochloric acid (1 M, 10 mL) was added. The aqueous layer was extracted with ethyl acetate (3×30 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue purified by silica column chromatography (methanol/dichloromethane, gradient from 0:100 to 10:90; R_f=0.6 (methanol/dichloromethane, 10:90)) followed by recrystallisation (ethyl acetate). Compound **8** was obtained as colourless plates (132 mg, 64%). Mp 176 °C. IR (KBr) cm^{-1}: 3300–3600, 1714, 1697, 1264, 1236. δ_H (400 MHz, acetone-d_6): 2.14 (1H, tt, *J* 6.4, 12.8 Hz, 2H, H6), 2.65 (2H, t, *J* 6.6 Hz, H7), 3.11 (2H, t, *J* 6.2 Hz, H5), 3.83 (3H, s, OMe), 7.54 (1H, dt, *J* 0.9, 8.0 Hz, H4), 8.14 (1H, d, *J* 8.0 Hz, H3), CO_2H proton not observed. δ_C (100 MHz, acetone-d_6): 22.5 (C6), 30.1 (C5), 39.2 (C7), 51.7 (OMe), 127.4 (C8a), 130.2 (C2), 130.3 (C4), 134.3 (C3), 136.4 (C1), 150.4 (C4a), 165.5 (CO_2H), 168.6 (CO_2Me), 195.9 (C8). MS (ESI) *m/z*: 271 ([M+Na]$^+$, 100%), 255 ([M+Li]$^+$, 100%). HRMS calcd for $C_{13}H_{12}O_5$ [M]$^+$: 248.0685. Found: 248.0688.

3.1.4. 1-(Isopropoxycarbonyl)-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (9). Pyridine (16.5 μL, 0.19 mmol) was added to a suspension of anhydride **7** (42 mg, 0.19 mmol) in 2-propanol (5 mL), and the mixture stirred under nitrogen at room temperature for 16 h. The solvent was removed under reduced pressure and aqueous hydrochloric acid (1 M, 5 mL) was added. The aqueous layer was extracted with ethyl acetate (3×15 mL), and the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue purified by silica column chromatography (methanol/dichloromethane, gradient from 0:100 to 10:90; R_f=0.4 (methanol/dichloromethane, 10:90)) followed by recrystallisation (ethyl acetate). Compound **9** was obtained as an amorphous white solid (32 mg, 60%). Mp 183 °C. IR (KBr) cm^{-1}: 3300–3600, 1732, 1701. δ_H (400 MHz, acetone-d_6): 1.32 (6H, d, *J* 6.0 Hz, CH_3), 2.14 (2H, tt, *J* 6.3, 12.6 Hz, H6), 2.66 (2H, t, *J* 6.8 Hz, H7), 3.11 (2H, t, *J* 6 Hz, H5), 5.26 (1H, sept, *J* 6.3 Hz, CH), 7.53 (1H, d, *J* 8.0 Hz, H4), 8.13 (1H, d, *J* 7.6 Hz, H3), 11.49 (1H, br s, CO_2H). δ_C (100 MHz, acetone-d_6): 21.0 (2×CH_3), 22.5 (C6), 30.2 (C5), 39.3 (C7), 67.9 (OCH), 127.4 (C2), 130.0 (C4), 130.2 (C8a), 134.3 (C3), 137.0 (C1), 150.2 (C4a), 165.5 (CO_2H), 167.4 (CO_2i-Pr), 195.7 (C8). MS (ESI) *m/z*: 299 ([M+Na]$^+$, 100%), 283 ([M+Li]$^+$, 100%). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.18; H, 5.83.

3.1.5. 1-[(*N*,*N*-Diethylamino)carbonyl]-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (11). Diethylamine (45 μL, 0.43 mmol) was added to a solution of anhydride **7** (94 mg, 0.43 mmol) in ethyl acetate (4 mL), and the mixture was stirred under nitrogen at room temperature for 16 h. The solvent was removed under reduced pressure and the residue recrystallised (ethyl acetate). Compound **11** was obtained as small yellow plates (99 mg, 80%). An analytically pure sample of **11** was prepared by further recrystallisation (ethyl acetate). Mp 172–174 °C. IR (KBr) cm^{-1}: 3300–3600, 1697, 1582. δ_H (400 MHz, acetone-d_6): 0.94 (3H, t, *J* 7.2 Hz, CH_3), 1.24 (3H, t, *J* 7.0 Hz, CH_3), 2.08–2.15 (2H, m, H6), 2.56–2.9 (2H, m, H7), 3.01 (2H, q, *J* 7.2 Hz, NCH_2), 3.07–3.10 (2H, m, H5), 3.44–3.57 (2H, m, NCH_2), 7.45 (1H, dt, *J* 0.8, 8.0 Hz, H4), 8.06 (1H, d, *J* 8.0 Hz, H3), CO_2H not observed. δ_C (100 MHz, acetone-d_6): 12.6 (CH_3), 13.7 (CH_3), 23.7 (C6), 31.6 (C5), 39.4 (NCH_2), 40.9 (C7), 43.6 (NCH_2), 129.2 (C2), 130.2 (C4), 131.3 (C8a), 135.6 (C3), 140.9 (C1), 151.0 (C4a), 167.4 (CO_2H), 169.2 (C(O)N), 197.3 (C8). MS (ESI) *m/z*: 290 ([M+H]$^+$, 93%), 296 ([M+Li]$^+$, 100%). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.54; H, 6.71; N, 4.58.

3.1.6. 1-[(*N*-Phenylamino)carbonyl]-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (12). Aniline (23 μL, 0.25 mmol) was added to a solution of anhydride **7** (54 mg, 0.25 mmol) in chloroform (3 mL, de-acidified with K_2CO_3) and the reaction mixture stirred under nitrogen at room temperature for 15 min. The reaction mixture was filtered and the solvent removed under reduced pressure. Compound **12** was obtained as an amorphous brown solid (77 mg, 99%). Mp 164–166 °C. IR (KBr) cm^{-1}: 3200–3500, 2929, 1693, 1596. δ_H (400 MHz, DMSO-d_6): 2.04 (2H, tt, *J* 6.4, 12.8 Hz, H6), 2.61 (2H, t, *J* 6.6 Hz, H7), 3.03 (2H, t, *J*

5.8 Hz, H5), 7.01 (1H, t, *J* 6.8 Hz, *p*-C_6H_5), 7.28 (2H, t, *J* 8.0 Hz, *m*-C_6H_5), 7.51 (1H, d, *J* 8.8 Hz, C4), 7.59 (2H, d, *J* 8.8 Hz, *o*-C_6H_5), 7.99 (1H, d, *J* 8.0 Hz, H3), 9.96 (1H, s, NH), CO_2H not observed. δ_C (100 MHz, acetone-d_6): 23.3 (C6), 31.0 (C5), 40.3 (C7), 120.5 (*o*-C_6H_5), 123.6 (*p*-C_6H_5), 129.1 (C2), 129.3 (*m*-C_6H_5), 130.5 (C4), 131.5 (C8a), 134.8 (C3), 140.1 (C1), 141.2 (*i*-C_6H_5), 150.4 (C4a), 166.8 (C(O)N), 167.4 (CO_2H), 196.8 (C8). MS (ESI) *m/z*: 310 ($[M+H]^+$, 58%), 316 ($[M+Li]^+$, 100%). HRMS calcd for $C_{18}H_{14}NO_4$ $[M-H]^-$: 308.0929. Found: 308.0928.

3.1.7. 1-[(*N*-Benzylamino)carbonyl]-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (13). Benzylamine (42 μL, 0.38 mmol) was added to a solution of anhydride **7** (82 mg, 0.38 mmol) in chloroform (3 mL, de-acidified with K_2CO_3), and the reaction mixture stirred under nitrogen at room temperature for 45 min. The reaction mixture was filtered and the solvent removed under reduced pressure. Compound **13** was obtained as an amorphous white solid (119 mg, 97%). Mp 140–142 °C. IR (KBr) cm^{-1}: 3200–3600, 3257, 1713, 1692, 1646. δ_H (400 MHz, DMSO-d_6): 2.02 (2H, tt, *J* 6.3, 12.6 Hz, H6), 2.60 (2H, t, *J* 6.6 Hz, H7), 2.99 (2H, t, *J* 5.8 Hz, H5), 4.39 (2H, d, *J* 5.6 Hz, NCH_2), 7.20–7.23 (1H, m, *p*-C_6H_5), 7.30 (2H, t, *J* 7.2 Hz, *m*-C_6H_5), 7.43 (1H, d, *J* 8.0 Hz, H4), 7.47 (2H, d, *J* 7.2 Hz, *o*-C_6H_5), 7.90 (1H, d, *J* 8.0 Hz, H3), 8.28 (1H, t, *J* 5.8 Hz, NH), 14.09 (1H, br s, CO_2H). δ_C (100 MHz, acetone-d_6): 23.4 (C6), 31.1 (C5), 40.5 (C7), 44.5 (NCH_2), 127.5 (*p*-C_6H_5), 128.9 (*o*-C_6H_5), 129.0 (*m*-C_6H_5), 129.8 (C2), 130.2 (C4), 131.8 (C8a), 134.6 (C3), 140.3 (C1), 140.6 (*i*-C_6H_5), 151.0 (C4a), 167.2 (CO_2H), 169.2 (C(O)N), 196.8 (C8). MS (ESI) *m/z*: 324 ($[M+H]^+$, 100%), 330 ($[M+Li]^+$, 74%). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.96; H, 5.33; N, 4.06.

3.1.8. 1-[(*N*-Morpholino)carbonyl]-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (14). Morpholine (16.6 μL, 0.19 mmol) was added to a solution of anhydride **7** (41 mg, 0.19 mmol) in ethyl acetate (3 mL). The mixture was stirred under nitrogen at room temperature for 3 h and the solvent removed under reduced pressure. The residue was purified by silica column chromatography (acetone/dichloromethane, gradient from 50:50 to 100:0; R_f=0.1 (acetone)). Compound **14** was obtained as an amorphous white solid (47 mg, 82%). Mp 202–206 °C. IR (KBr) cm^{-1}: 3300–3600, 1718, 1688, 1591. δ_H (400 MHz, acetone-d_6): 2.13 (2H, tt, *J* 6.5, 13.0 Hz, H6), 2.59–2.71 (2H, m, H7), 2.96–3.05 (2H, m, NCH_2), 3.07–3.11 (2H, m, H5), 3.50 (2H, t, *J* 5.0 Hz, OCH_2), 3.57–3.80 (4H, m, OCH_2, NCH_2), 7.48 (1H, dt, *J* 0.9, 8.0 Hz, H4), 8.08 (1H, d, *J* 8.0 Hz, H3), CO_2H proton not observed. δ_C (100 MHz, DMSO-d_6): 22.1 (C6), 29.7 (C5), 39.2 (C7), 41.2 (NCH_2), 46.0 (NCH_2), 65.2 (OCH_2), 65.3 (OCH_2), 128.2 (C2), 129.4 (C8a), 129.4 (C4), 134.0 (C3), 137.5 (C1), 149.6 (C4a), 166.6 (C(O)N), 167.3 (CO_2H), 197.8 (C8). MS (ESI) *m/z*: 304 ($[M+H]^+$, 100%), 326 ($[M+Na]^+$, 36%), 310 ($[M+Li]^+$, 100%). HRMS calcd for $C_{16}H_{16}NO_5$ $[M-H]^-$: 302.1034. Found: 302.1029.

3.1.9. 1-[(*N*-Thiopentyl)carbonyl]-8-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (15). A solution of anhydride **7** (100 mg, 0.46 mmol) in dichloromethane (2 mL) was added dropwise to pentane-1-thiol (286 μL, 2.31 mmol) and pyridine (187 μL, 2.31 mmol) in dichloromethane (5 mL). The resulting reaction solution was stirred under nitrogen at room temperature for 16 h. The solvent was removed under reduced pressure and aqueous hydrochloric acid (1 M, 15 mL) was added. The aqueous layer was extracted with ethyl acetate (3×30 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and the residue purified by silica column chromatography (ethyl acetate/dichloromethane, gradient from 0:100 to 50:50) followed by high-pressure liquid chromatography (5 m Hypersil® BDS C18 250×10 mm column; t_R 16 min; H_2O/CH_3CN with 0.2% TFA gradient: 60:40 for 20 min then 40:60 for 5 min). Compound **15** was obtained as an amorphous white solid (32 mg, 60%). Mp 184–187 °C. IR (KBr) cm^{-1}: 3300–3600, 1703, 1686, 1676. δ_H (400 MHz, acetone-d_6): 0.92 (3H, t, *J* 6.8 Hz, H5′), 1.38–1.46 (4H, m, H3′, H4′), 1.75 (2H, tt, *J* 7.4, 14.8 Hz, H2′), 2.15 (2H, tt, *J* 6.4, 12.8 Hz, H6), 2.65 (2H, t, *J* 6.6 Hz, H7), 3.04 (2H, t, *J* 7.2 Hz, H1′), 3.12 (2H, t, *J* 6.2 Hz, H5), 7.58 (1H, d, *J* 8.4 Hz, H4), 8.09 (1H, d, *J* 8.0 Hz, H3), CO_2H not observed. δ_C (100 MHz, acetone-d_6): 14.25 (C5′), 22.90 (C4′), 23.15 (C6), 29.35 (C2′), 30.05 (C1′), 30.88 (C5), 31.87 (C3′), 40.10 (C7), 128.89 (C2), 131.15 (C8a), 131.48 (C4), 134.83 (C3), 142.24 (C1), 150.89 (C4a), 166.18 (CO_2H), 193.31 (C(O)S), 195.99 (C8). MS (ESI) *m/z*: 327 ($[M+Li]^+$, 18%), 343 ($[M+Na]^+$, 100%). HRMS calcd for $C_{17}H_{20}SO_4Na$ $[M+Na]^+$: 343.0975. Found: 343.0981.

3.1.10. 1-Phenyl-8a-hydroxy-2-oxo-1,2,6,7,8,8a-hexahydrobenzo[*cd*]indole-3-carboxylic acid (16). Phenylamide **12** (26 mg, 0.08 mmol) was stirred under nitrogen in acetone (5 mL) at room temperature for 48 h. The reaction solution was filtered and the solvent removed. Compound **16** was obtained as an amorphous white solid (25 mg, 96%) with <5% of **18** present (cf. ^1H NMR δ 5.81). Mp 171–173 °C. IR (KBr) cm^{-1}: 3300–3600, 1701, 1618, 1589, 1451. ^1H NMR (400 MHz, acetone-d_6) δ: 1.75–1.83 (1H, m, H8), 2.07–2.12 (1H, m, H7), 2.30–2.44 (2H, m, H8, H7), 2.86–2.94 (1H, m, H6), 3.12–3.22 (1H, m, H6), 5.90 (1H, d, *J* 2.4 Hz, OH), 7.46 (1H, dt, *J* 1.8, 7.5 Hz, *p*-C_6H_5), 7.54 (2H, t, *J* 7.8 Hz, *m*-C_6H_5), 7.63–7.68 (3H, m, H5, *o*-C_6H_5), 14.65 (1H, br s, CO_2H). δ_C (100 MHz, acetone-d_6): 19.8 (C7), 25.6 (C6), 31.4 (C8), 90.6 (C8a), 127.8 (C3), 128.2 (C2a), 128.7 (*o*-C_6H_5), 129.4 (*p*-C_6H_5), 130.5 (*m*-C_6H_5), 134.0 (C5), 135.4 (C4), 136.4 (*i*-C_6H_5), 142.1 (C5a), 146.6 (C8b), 165.6 (CO_2H), 170.9 (C2). MS (ESI) *m/z*: 310 ($[M+H]^+$, 100%), 332 ($[M+Na]^+$, 100%), 316 ($[M+Li]^+$, 100%). HRMS calcd for $C_{18}H_{14}NO_4$ $[M-H]^-$: 308.0929. Found: 308.0918.

3.1.11. 1-Benzyl-8a-hydroxy-2-oxo-1,2,6,7,8,8a-hexahydrobenzo[*cd*]indole-3-carboxylic acid (17). Benzylamine (74 μL, 0.68 mmol) was added to a solution of anhydride **7** (146 mg, 0.68 mmol) in ethyl acetate (5 mL), and the reaction mixture stirred under nitrogen at room temperature for 1 h. The solvent was removed under reduced pressure and the residue recrystallised (ethyl acetate). Compound **17** was obtained as an amorphous white solid (159 mg, 72%). Mp 184 °C. IR (KBr) cm^{-1}: 3300–3500, 1622, 1463, 1454. δ_H (400 MHz, DMSO-d_6): 1.11–1.19 (1H, m, H8), 1.81–1.91 (1H, m, H7), 2.01–2.06 (1H, m,

H8), 2.10–2.21 (1H, m, H7), 2.69–2.77 (1H, m, H6), 2.98–3.05 (1H, m, H6), 4.48 (1H, d, *J* 15.6 Hz, NCH_2), 4.93 (1H, d, *J* 16.0 Hz, NCH_2), 6.63 (1H, s, OH), 7.24–7.38 (5H, m, C_6H_5), 7.59 (1H, d, *J* 8.0 Hz, H5), 8.04 (1H, d, *J* 8.0 Hz, H4), 14.6 (1H, br s, CO_2H). δ_C (100 MHz, DMSO-d_6): 18.0 (C7), 23.8 (C6), 30.2 (C8), 42.2 (NCH_2), 87.0 (C8a), 125.3 (C3), 126.4 (C2a), 127.3 (*o*-C_6H_5), 127.7 (*m*- or *p*-C_6H_5), 128.4 (*m*- or *p*-C_6H_5), 132.3 (C5), 132.9 (C4), 137.3 (*i*-C_6H_5), 140.2 (C5a), 145.2 (C8b), 164.7 (CO_2H), 169.1 (C(O)N). MS (ESI) *m/z*: 324 ($[M+H]^+$, 100%), 346 ($[M+Na]^+$, 89%), 330 ($[M+Li]^+$, 100%). HRMS calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1236. Found: 324.1230.

3.1.12. 1-Benzyl-8a-hydroxy-2-oxo-1,2,6,7,8,8a-hexahydrobenzo[*cd*]indole-3-carboxylic acid (17). Amide **13** (6 mg, 0.019 mmol) was stirred under nitrogen in ethyl acetate (1 mL, de-acidified) at room temperature for 48 h. The reaction solution was filtered and the solvent removed. Compound **17** was obtained as a white solid (5.95 mg, 99%).

3.1.13. 1-Phenyl-2-oxo-1,2,6,7-tetrahydrobenzo[*cd*]indole-3-carboxylic acid (18). Lactamol **16** (80 mg, 0.26 mmol) was stirred with one drop of hydrochloric acid under nitrogen in chloroform (4 mL) at room temperature for 16 h. The reaction solution was diluted with chloroform (20 mL), washed with brine (20 mL), dried ($MgSO_4$) and filtered. The solvent was removed and the residue purified by silica column chromatography (dichloromethane/ethyl acetate, gradient from 100:0 to 0:100; R_f=0.6 (dichloromethane/ethyl acetate, 90:10)). Compound **18** was obtained as an amorphous white solid (59 mg, 78%) in approximately 95% purity. Mp 143–146 °C. IR (KBr) cm^{-1}: 3300–3600, 1726, 1622. δ_H (400 MHz, acetone-d_6): 2.88 (2H, dt, *J* 4.1, 8.0 Hz, H7), 3.20 (2H, t, *J* 7.6 Hz, H6), 5.82 (1H, t, *J* 4.4 Hz, H8), 7.50–7.53 (1H, m, C_6H_5), 7.58–7.64 (4H, m, C_6H_5), 7.68 (1H, dd, *J* 7.2, 1.6 Hz, H5), 8.20 (1H, d, *J* 7.2 Hz, H4), CO_2H not observed. δ_C (100 MHz, acetone-d_6): 24.27 (C7), 24.48 (C6), 110.08 (C8), 122.67 (C2a), 126.63 (C3), 127.69 (*o*- or *m*-C_6H_5), 129.22 (*p*-C_6H_5), 130.25 (*o*- or *m*-C_6H_5), 131.91 (C5), 134.70 (*i*-C_6H_5), 134.89 (C4), 135.01 (C8b), 135.43 (C8a), 138.64 (C5a), 164.84 (C(O)N), 169.79 (CO_2H). MS (ESI) *m/z*: 292 ($[M+H]^+$, 100%), 298 ($[M+Li]^+$, 89%). HRMS calcd for $C_{18}H_{14}NO_3$ $[M+H]^+$: 292.0968. Found: 292.0972.

3.1.14. 1-Benzyl-2-oxo-1,2,6,7-tetrahydrobenzo[*cd*]indole-3-carboxylic acid (19). Lactamol **17** (100 mg, 0.31 mmol) was stirred with two drops of hydrochloric acid under nitrogen in chloroform (5 mL) at room temperature for 4 h. The reaction solution was diluted with chloroform (20 mL), washed with brine (20 mL), dried ($MgSO_4$) and filtered. The solvent was removed and the residue recrystallised (ethyl acetate). Compound **19** was obtained as small pale yellow plates (67 mg, 72%). An analytical pure sample of **19** was prepared by further recrystallisation (ethyl acetate). Mp 198–200 °C. IR (KBr) cm^{-1}: 3200–3600, 1716, 1616. δ_H (400 MHz, acetone-d_6): 2.82 (2H, dt, *J* 4.1, 8.0 Hz, H7), 3.11 (2H, t, *J* 8.2 Hz, H6), 5.11 (2H, s, NCH_2), 5.96 (1H, t, *J* 4.4 Hz, H8), 7.28–7.43 (5H, m, C_6H_5), 7.60 (1H, d, *J* 7.6 Hz, H5), 8.13 (1H, d, *J* 7.6 Hz, H4), 14.13 (1H, br s, CO_2H). δ_C (100 MHz, acetone-d_6): 24.80 (C7), 24.91 (C6), 45.21 (NCH_2), 110.17 (C8), 123.39 (C2a), 127.21 (C3), 129.08 (*o*-C_6H_5), 129.14 (*p*-C_6H_5), 130.16 (*m*-C_6H_5), 132.20 (C5), 135.05 (C8a), 135.10 (C4), 135.53 (C8b), 137.98 (*i*-C_6H_5), 138.97 (C5a), 165.58 (CO_2H), 171.00 (C(O)N). MS (ESI) *m/z*: 306 ($[M+H]^+$, 36%), 328 ($[M+Na]^+$, 89%), 312 ($[M+Li]^+$, 100%). Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.56; H, 4.82; N, 4.63.

3.2. Reactivity investigation—anhydride 7 versus phthalic anhydride 20

Diethylamine ((i) 2 equiv, (ii) and (iii) 1 equiv) was added to a solution of anhydride **7** ((i) 1 equiv, (ii) 2 equiv or (iii) 10 equiv) and phthalic anhydride **20** ((i) 1 equiv, (ii) 2 equiv or (iii) 10 equiv) in ethyl acetate, and the mixture was stirred under nitrogen at room temperature for 16 h. The crude product mixtures were dried under high vacuum and the ^1H NMR spectra obtained using acetone-d_6 as solvent. Integration of the baseline-resolved peaks at δ 1.02 ppm (CH_3 for 2-(diethylcarbamoyl)benzoic acid **21**[37]), 7.45 ppm (H4 for amide **11**), 8.06 ppm (H4 for anhydride **7**) and 8.05–8.11 ppm (for the sum of H4–7 for phthalic anhydride **20** plus H4 for **7**, plus H3 for **11**, plus H2–6 for **21**) was used to calculate the percentage composition of these components from the integral of the total crude mixture.

3.3. Crystal data for 19

Crystallised by slow evaporation from toluene. $C_{19}H_{15}NO_3$ M=305.3, monoclinic, space group $P2_1/c$, a=9.958(3), b=18.917(7), c=8.333(2) Å, β=107.36(2)°, U=1498.2(8) $Å^3$, Z=4, D_c=1.35g cm^{-3}, crystal size: 0.40×0.30×0.25 mm, 2976 reflections collected, 2627 unique (R_{int}=0.049), R=0.049 [1778 reflections with $I>2\sigma(I)$], $wR(F^2)$=0.153 (all data). Crystallographic data for the structural analysis of **19** has been deposited with the Cambridge Crystallographic Data Centre CCDC no. 608262.

Acknowledgements

Financial support for this work was provided by (1) Griffith University, (2) Natural Product Discovery, Griffith University and (3) the Eskitis Institute for Cell and Molecular Therapies, Griffith University.

Supplementary data

Supplementary data available: (a) general procedures and experimental procedures for compounds **1**, **3** and **5**; (b) ^1H NMR spectra for compounds **7**, **8**, **12**, **14**, **16** and **17**; (c) X-ray crystallographic data collection, structure solution, refinement of **19**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.090.

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