Pergamon

Tetrahedron 58 (2002) 975–982

TETRAHEDRON

The reactivities of dehydroalanine derivatives towards 1,3-dienyl cobaloxime complex: new routes to functionalised carbocyclic amino acids

Christina L. L. Chai,* Ruth C. Johnson and Jerome Koh

Department of Chemistry, Australian National University, Canberra, ACT 0200, Australia

Received 5 August 2001; revised 1 November 2001; accepted 15 November 2001

Abstract—The reactivities and selectivities of the Diels–Alder reactions of acyclic dehydroalanine esters and cyclic dehydroalanines derived from piperazine-2,5-diones with 1,3-dienyl cobaloxime complex are reported. From our studies we demonstrate the use of the activated organocobalt diene in a 'combinatorial' approach to the synthesis of functionalised cyclic amino acids and derivatives from a single cycloaddition reaction.

1. Introduction

An emerging important class of non-proteinogenic amino acids is the cyclic amino acids which display diverse biological effects, ranging from inhibition of enzymes such as *S*-adenosyl L-methionine synthase[1] to behaviour as agonists and/or antagonists with biological receptors.[2] More recently, the design and synthesis of conformationally constrained cyclic amino acids have attracted attention due to the potential use of these compounds as peptidomimetics.[3] In some cases, replacement of a natural amino acid with a cyclic amino acid in a peptide sequence leads to modification of biological activity due to restriction in the conformational freedom of the peptide. This in turn may result in high potency/selectivity of these peptides with biological receptors and increased stability with respect to enzymatic degradation.

Historically cyclic amino acids are synthesised via the Strecker or Bucherer–Lieb synthesis,[4] but recent strategies employ cycloaddition reactions of dehydroalanine derivatives.[5] The former two methods are not amenable to rapid carboskeletal modifications as the cyclic carbon framework is generally installed prior to the synthesis of the amino acid. The latter method involving Diels–Alder (DA) cycloadditions of dehydroalanine derivatives is clearly more versatile. However, the existing systems frequently require harsh reaction conditions (high temperatures, Lewis catalysts) to increase reactivities, and purification is often difficult due to cyclodimerisation of the dienes as well as difficulties in the removal of catalysts and byproducts.[6] As part of our continuing studies to develop more efficient and selective strategies to this class of amino acids,[7] we were attracted by recent reports where stoichiometric organocobalt(III) dienyl complexes were utilised as means to improve the reactivities and selectivities of homo- and hetero-DA reactions.[8] Our studies reported herein outline the scope and limitations of cycloaddition reactions of dehydroalanine derivatives with a 1,3-dienyl cobaloxime derivative. In addition, we demonstrate that this synthetic method allows for a 'combinatorial' approach to the synthesis of functionalised adducts from a single cycloaddition reaction.

2. Results and discussion

In order to exploit the synthetic potential of dehydroamino derivatives as dienophiles, a clear understanding of the reactivity and selectivity patterns observed in the DA reactions are desired. Our studies thus commenced with an assessment of the factors that affect the reactivity of cycloaddition reactions of dehydroalanine derivatives. In the course of this study, acyclic dehydroamino esters, synthesised following modification of literature procedures, were used. As our previous studies have shown that cyclic dehydroalanine derivatives such as methylidene piperazinediones are superior dienophiles with potential applications as chiral templates,[9] the reactivity and selectivity of these cyclic dehydroalanine derivatives were also examined. Methods for cleavage of piperazine-2,5-diones to the constituent α-amino acids are well established[10] and hence through these systems stereoselective routes to the synthesis of cyclic amino acids are possible.

Keywords: amino acids and derivatives; Diels–Alder.

* Corresponding author. Fax: +61-26125-0760;
e-mail: christina.chai@anu.edu.au

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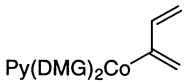
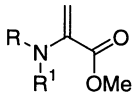
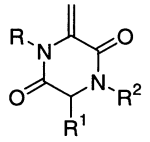
PII: S0040-4020(01)01160-7



(1)



(2a) R=Ac, R^1=H
(2b) R=TFA, R^1=H
(2c) R=Boc, R^1=H
(2d) R=R^1=Phthaloyl

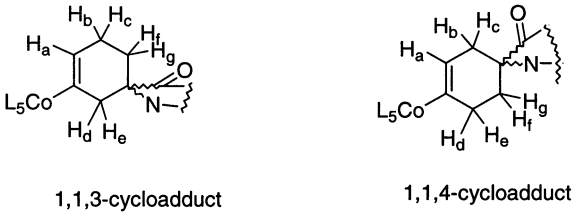


(3a) R=R^2=Ac, R^1=H
(3b) R=R^1=H, R^2=Ac
(3c) R=H, R^1=Me, R^2=Ac
(3d) R=R^2=Ac, R^1=Me

2.1. Reactivity of Diels–Alder reactions of acyclic dehydroalanine esters

The reactivities of the Diels–Alder cycloadditions between cobalt diene **1** and the acyclic dehydroalanine derivatives **2a**–**2d** were assessed at room temperature and at 62°C (reflux temperature for chloroform) (Scheme 1, Table 1). The cycloadditions were typically performed under nitrogen in rigorously degassed chloroform, using equimolar amounts of diene and dienophile. With the exception of the *N*-trifluoroacetyl (*N*-TFA) dehydroalanine ester **2b**, cycloaddition reactions of the dehydroalanine esters with the organocobaloxime **1** at room temperature were extremely sluggish and only trace amounts (<10%) of conversion to the cycloadducts were observed (Table 1). With the *N*-TFA derivative, 44% conversion to the cycloadduct was observed while at reflux temperature, the degree of conversion was lower (37%) due to decomposition of the dienophile. Decomposition of the *N*-acetyl (*N*-Ac) dehydroalanine ester **2a** was also observed upon heating and with dehydroalanine esters **2c**, **2d**, no significant increase in the conversion to products was noted. Interestingly, under reflux conditions, when the concentration of the *N*-phthaloyl (*N*-Pht) dehydroalanine ester **2d** was increased considerably, cycloadduct **4d** was obtained in 51% yield.

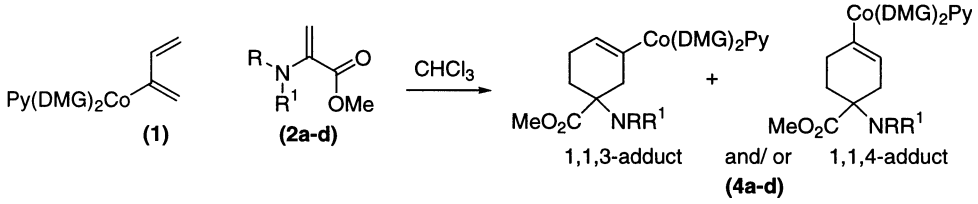
Although two regioisomers can result from the cycloaddition reactions of organocobalt diene **1** with the dienophiles **2b**, **2d**, in both cases only one regioisomer was detected in the ^{1}H NMR spectra of the crude reaction mixtures. The regiochemistry of cycloaddition was determined using two-dimensional (2-D) H–H correlation NMR spectroscopy (COSY). In the COSY spectra, the cycloadducts show correlations between the olefinic proton H_a and the adjacent allylic protons H_b, H_c (see Fig. 1) As these allylic protons do not show correlations with any of the remaining four cycloaliphatic proton resonances, the correlation pattern displayed is consistent with the 1,1,4-substituted regioisomer. If the 1,1,3-substitution pattern was present instead, the allylic protons H_b, H_c would show strong correlation to the adjacent two homoallylic protons H_f, H_g.



1,1,3-cycloadduct 1,1,4-cycloadduct

Figure 1.

The observed regioselectivity of cycloaddition with organocobalt diene **1** can be readily rationalised in terms of orbital coefficients. Using AM1 calculations,[11] the orbital coefficient of the disubstituted carbon atom of the olefin in the dienophile was found to be consistently smaller than that of the unsubstituted carbon atom of the olefin. On this basis,



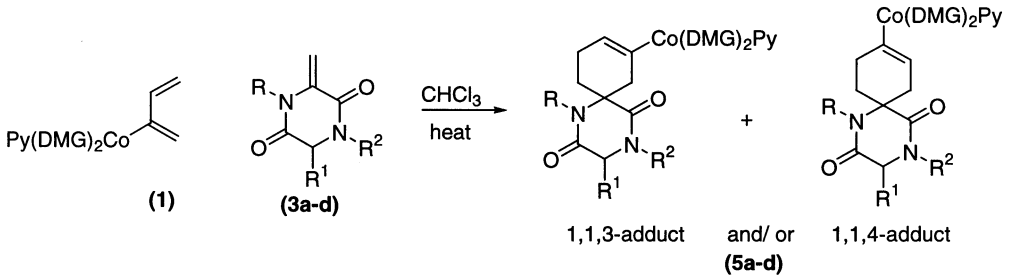
(1) (2a-d) 1,1,3-adduct and/ or 1,1,4-adduct (4a-d)

Scheme 1.

Table 1. Reactions of acyclic dehydroamino esters **2a**–**2d** with organocobaloxime complex **1**

	% Conversion and/or [isolated yields] to cycloadducts			
	N-Ac **2a**	*N*-TFA **2b**	*N*-Boc **2c**	*N*-Pht **2d**
rt, 14 days	5–6 [n.a.]	44 [n.a.]	<5 [n.a.]	5–7 [n.a.]
Reflux (62°C, 16 h)	Decomp. [n.a.]	37 with decomp. [15%]	<5 [n.a.]	52[a] [51%][a]

n.a.—Cycloadduct was not isolated (see Section 3).
[a] Obtained under high concentration conditions.



Scheme 2.

Table 2. Reactions of cyclic dehydroamino derivatives **3a–3d** with organocobaloxime complex **1**

	% Conversion and/or [isolated yields] to cycloadducts			
	N,N-diAc Gly **3a**	*N*-Ac Gly **3b**	*N*-Ac Ala **3c**	*N,N*-diAc Ala **3d**
rt, 14 days	60[a] [n.a.]	>95 [68%]	60 [n.a.]	80[b] [53%][b]
Reflux (62°C, 16 h)	75[a] [65% of **5a**]	>95 [60%]	60 [55%]	75[c] [70%][c]

n.a.—Cycloadduct was not isolated (see Section 3).
[a] Combined % conversion to di- and mono-acetylated cycloadduct **5a**, **5b**.
[b] Reaction was carried out at room temperature for 14 days in THF and yields the *N,N*-diacetylated cycloadduct **5d**.
[c] Reaction only yields the mono acetylated cycloadduct **5c**.

greatest matching of orbitals with orbital coefficients of the electron rich cobalt diene **1** arise when the 1,1,4- orientation is achieved. This is consistent with the experimental observations.

2.2. Reactivity of Diels–Alder reactions of cyclic dehydroalanine derivatives

In contrast to the poor reactivities of acyclic dehydroalanine esters towards cycloaddition reactions with organocobaloxime **1**, the cyclic dehydroalanine derivatives **3a–3d** show good conversions to cycloadducts at 62°C for 16 h (see Scheme 2, Table 2). Similar to higher degrees of conversions are observed when the reactions are carried out at room temperature over 14 days.

Reactions of the *N,N′*-diacetylated methylidene piperazinedione **3a** with the organocobalt diene **1** gave two adducts in the ratio of 7:1. The major product was identified as the *N,N′*-diacetyl cycloadduct **5a** while the minor product was identified as the monoacetyl cycloadduct **5b** by comparison with an authentic sample derived from the reaction of monoacetylated methylidene piperazinedione **3b**.

Under similar reflux conditions, the reaction of *N,N′*-diacetylated alanyl derived piperazinedione **3d** with cobalt diene **1** gave only the monoacetylated cycloadduct **5c**. This monoacetylated cycloadduct was identical in all respects to the cycloadduct derived from the reaction of monoacetylated methylidene piperazinedione **3c** with cobalt diene **1**. The diacetylated cycloadduct **5d** can be obtained from methylidene piperazinedione **3d** in high yields by carrying out the reaction at room temperature in THF. In all the cases above, the Diels–Alder reactions are highly selective—only one isomer was detected in the ^{1}H and ^{13}C NMR spectra of the crude reaction mixtures. Thus as in the acyclic systems, the cycloaddition reactions were highly regioselective for the 1,1,4-regioisomer as determined by 2-D NMR spectroscopy techniques. In addition, the Diels–Alder reactions with the chiral methylidene piperazinedione **3c** and **3d** are highly stereoselective. The stereochemistries of the cycloadduct **5c**, **5d** were determined by nOe experiments, which showed correlations between the remote α-methyl signals at 1.5 ppm and the H_g signal previously identified via HMQC experiments. (Fig. 2) This suggests that the approach of the diene is *anti* to the remote α-methyl substituent. The stereoselectivity of the Diels–Alder reaction between the cobalt diene **1** and the chiral methylidene piperazinediones **3c**, **3d** may be rationalised in terms of the directing effect of the remote α-methyl substituent. Thus, the approach of the diene to the *Si* face of the dienophile is sterically hindered, and the attack of the diene occurs preferentially at the *Re* face to yield the *anti* cycloadduct **5c**, **5d**.

It is interesting to note that the stereochemical outcomes for

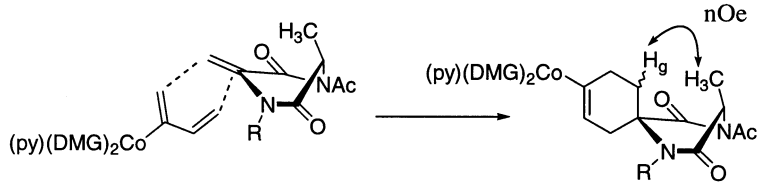


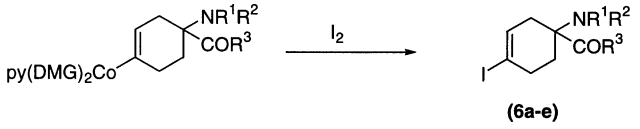
Figure 2.

the Diels–Alder reaction of alanyl derived methylidene piperazinedione **3c**, **3d** depends on the nature of the diene used. From our previous studies, we have shown that with cyclopentadiene as the diene, facial selectivity (*Si*/*Re*) is only marginal (1.7:1) when methylidene piperazinedione **3c** was used as dienophile.[9] In contrast, our studies here show that the reaction of methylidene piperazinedione **3c** with the cobalt diene **1**, high facial selection is observed. This is presumably due to the large steric bulk of the cobaloxime ligand which disfavours the approach from the *Si* face of the olefin.

2.3. Application to the synthesis of functionalised amino acids: cleavage studies

To demonstrate the versatility of the cycloaddition reactions to the synthesis of cyclic amino acids, the cobalt–carbon bonds of the cycloadducts were cleaved under a variety of conditions. Cleavage of the cobalt–carbon bond with iodine was attempted on all of the isolated cycloadducts, and the corresponding vinyl iodides **6b–6e** were obtained in yields ranging from 62–88%.

Low yields were obtained for the *N*-TFA iodide **6a** and hence isolation of the iodide was not attempted. The vinyl iodides are characterised by the downfield shift of the olefinic ^{1}H NMR resonance from 5.0–5.3 ppm in the cycloadduct to 6.3–6.4 ppm in the iodide. The results are summarised in Scheme 3, Table 3 below.



Scheme 3.

Table 3. Conversion of cobalt cycloadducts to the corresponding vinyl iodides

Cycloadduct	Vinyl iodide	Isolated yields (%)
4b	**6a**	n.a.
4d	**6b**	88
5a	**6c**	65
5b	**6d**	64
5c	**6e**	62

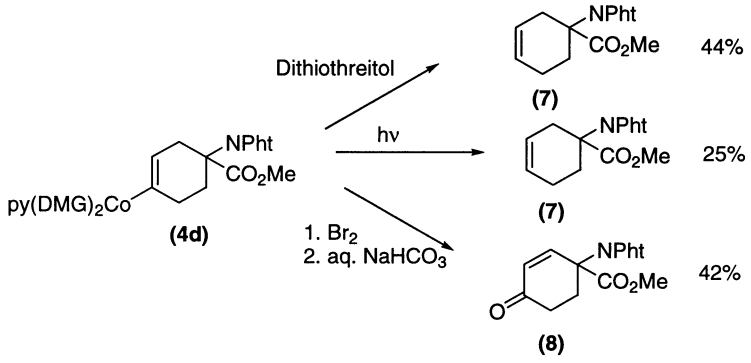
Other demetalation methods also lead to functionalised cyclic amino acid derivatives and this is illustrated with the conversion of a single cobalt cycloadduct **4d** to derivatives **7**, **8** (Scheme 4). Thus, as noted by Welker and co-workers, organocobaloxime dienes serve as synthetic equivalents to a range of dienes (e.g. butadiene, Daniefshiesky diene, 2-OTMS butadiene) depending on the method of cleavage.[8] Corresponding reactions of dehydroalanines with butadiene and derivatives are difficult and frequently require harsh reaction conditions and/or prolonged reaction times.[12] The use of the activated organocobaloxime dienyl complex as the synthetic diene equivalent is very attractive and adds to the versatility and scope of the Diels–Alder reaction of dehydroalanines as applied to the synthesis of cyclic amino acids. It can also be envisaged that the post-cleavage products can be further transformed to other new structures, thus increasing the synthetic utility of the cobalt cycloadducts. For example, the vinyl iodide derivatives **6** are potential substrates for further carbon–carbon bond formation reactions via transition-metal catalysed coupling reactions.

With the use of chiral methylidene piperazinediones **3c**, **3d**, the methodology as outlined above can be applied to the asymmetric synthesis of functionalised cyclic amino acids. The use of this chiral template enhances both the reactivity of the dehydroalanine moiety as well as direct the stereochemical outcome of the reactions.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini II 300 MHz spectrometer, operating at 300 MHz for proton and 75 MHz for carbon spectroscopy. Double quantum ^{1}H–^{1}H correlation spectroscopy (DQCOSY) NMR experiments were carried out on a Varian Inova 500 spectrometer (500 MHz). All 1-D and 2-D ^{1}H NMR spectra were recorded in $CDCl_3$, CD_2Cl_2 or CD_3OD as stated, using the residual solvent peaks at 7.26 ppm ($CHCl_3$), 5.32 ppm ($CHDCl_2$) and 3.30 ppm (CD_2HOD) as internal references. ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_2Cl_2 as stated, using the respective residual solvent peaks at 77 ppm ($CDCl_3$) and 53.8 ppm ($CHDCl_2$) as internal references. All chemical shifts are reported as δ values in parts per million (ppm).



Scheme 4.

Infrared spectra were recorded on a Perkin–Elmer Spectrum One spectrophotometer and samples were analysed as KBr discs. Microanalyses and mass spectra were performed by the Analytical Facility of the Australian National University. Melting points were recorded on an Electrothermal melting point apparatus and Leica MV TG micro hot stage apparatus and are uncorrected.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} (supplied by Merck) and the chromatograms were visualised under a 254 nm UV lamp and by treatment with a developing solution (Ammonium molybdate/ceric(IV) ammonium sulfate/sulfuric acid/water (10 g:0.4 g:5.6 mL:200 mL) dip] followed by heating. Column chromatography was conducted using Merck silica gel 60 (230–400 mesh ASTM) and analytical reagent (AR) grade solvents. Analytical grade solvents (AR) were used as received or purified before use according to Armarego and Perrin.[13]

Dehydroamino esters **2a**–**2d**,[14] methylidene piperazinediones **3a**–**3d**[15] and organocobaloxime dienyl complex **1**[8a,b] were synthesised following literature procedures.

3.2. General procedures for Diels–Alder reactions

NOTE! Reactions involving organocobalt compounds should be conducted in the dark to minimise photodecomposition.

3.2.1. General procedure for Diels–Alder cycloadditions under room temperature conditions. To a solution of cobalt diene **1** (20 mg, 0.47 mmol) in degassed deuterated chloroform (0.5 mL) in an NMR tube was added one equivalent of dienophile (0.47 mmol). The NMR tube was flushed with N_2 and the reaction mixture was kept in the dark. The NMR spectrum of the reaction mixture was recorded at regular intervals to monitor the progress of the reaction. After 14 days the extent of cycloaddition was recorded by careful integration of the appropriate signals in the ^{1}H NMR spectrum.

When the reaction was carried out on a synthetic scale (concentration of cobalt diene **1** typically 100 mg/5 mL chloroform), the desired cycloadduct was isolated by firstly removing the solvent under reduced pressure, followed by trituration of the residue with methanol. The resulting yellow precipitate was further purified using either column or radial chromatography.

The degree of conversion as monitored by NMR spectroscopy and the isolated yields of the cycloadducts are tabulated in Tables 1 and 2.

3.2.2. General procedure for Diels–Alder cycloadditions under heating conditions. To a solution of cobalt diene **1** in degassed chloroform (typically 100 mg/5 mL chloroform) was added 1 equiv. of dienophile while stirring under N_2 in the dark The reaction mixture was refluxed under N_2 and the progress of the reaction was monitored by TLC. After consumption of the diene or until no further reaction was detected (typically 16 h), the reaction mixture was concentrated under reduced pressure and the extent of conversion was determined by ^{1}H NMR spectroscopy. The residue was triturated with methanol and the resulting precipitate was collected by vacuum filtration. The precipitated cycloadduct was further purified by column chromatography.

The degree of conversion as monitored by ^{1}H NMR spectroscopy and the isolated yields of the cycloadducts are tabulated in Tables 1 and 2.

3.3. Data for Diels–Alder cycloadducts

3.3.1. [(1-Carbomethoxy-1-trifluoroacetylaminocyclohex-3-en-4-yl)pyridine bis (dimethylglyoximato)] cobalt(III) (4b). Chromatography: 1:1 dichloromethane/diethyl ether, R_f 0.33, isolated as an orange solid. Mp 180°C dec. ^{1}H NMR. ($CDCl_3$): δ 1.70–2.40 (m, 5H, cyclohexene ring protons); 2.08 (s, 6H, DMG methyl group); 2.10 (s, 6H, DMG methyl group); 2.62 (d, 1H, J=15 Hz, cyclohexene ring proton); 3.69 (s, 3H, CO_2CH_3); 5.10 (d, 1H, J=6 Hz, olefinic proton); 6.49 (s, 1H, N*H*); 7.31 (t, 2H, H-3 py); 7.71 (t, 1H, H-4 py); 8.59 (d, 2H, J=5 Hz, H-2 py). ^{13}C NMR ($CDCl_3$): δ 12.0 (DMG CH_3); 28.1 (cyclohexene ring CH_2); 28.8 (cyclohexene ring CH_2); 36.5 (cyclohexene ring CH_2); 52.6 (OCH_3); 58.2 (cyclohexene ring C(NHTFA)(CO_2CH_3); 117.8 (olefinic *C*H); 125.3 (*C*-3 py); 137.7 (*C*-4 py); 149.8 (DMG *C*=N); 149.9 (*C*-2 py); 150.3 (DMG *C*=N); 172.4 (CO_2CH_3); CF_3, *C*Co and $COCF_3$ quaternary resonances not seen. FAB-MS: (*m/z*, %) 619 (MH^+, 20%), 562 (MH^+-3F, 10%), 539 (M^+-py, 100%). IR (cm^{-1}): 3427 (NOH, str.), 1742 (ester C=O, str.), 1717 (trifluoroacetyl C=O, str.), 1563 (med.), 1230 (str.), 1185 (str.), 1156 (str.), 1089 (str.). Microanalysis: Calcd for $C_{23}H_{30}F_3N_6O_7Co$: C, 44.67; H, 4.89. Found: C, 44.30; H, 5.11.

3.3.2. [(1-Carbomethoxy-1-(1′,3′-dioxo-1′,3′-dihydroisoindol-2′-yl)-cyclohex-3-en-4-yl) pyridinebis(dimethylglyoximato)]cobalt(III) hydrate (4d). For the reaction carried out under reflux conditions, the amount of solvent used was reduced to 1 mL of chloroform per 100 mg of diene.

Chromatography: ethyl acetate, R_f 0.5, isolated as an orange solid. Mp 200°C dec. ^{1}H NMR ($CDCl_3$): δ 1.59 (br s, 2H, lattice water); 1.80–2.20 (m, 3H, cyclohexene ring protons); 1.92 (s, 6H, DMG methyl protons); 2.11 (s, 6H, DMG methyl protons); 2.62–2.69 (m, 2H, cyclohexene ring protons); 3.27 (d, 1H, J=15 Hz, allylic ring proton); 3.65 (s, 3H, CO_2CH_3); 5.22 (m, 1H, olefinic proton); 7.27 (m, obscured by solvent peak, 2H, H-3 py); 7.60–7.80 (m, 5H, aromatic ring protons and H-4 py); 8.62 (d, 2H, J=5 Hz, H-2 py). ^{13}C NMR ($CDCl_3$): δ 11.9 (DMG CH_3); 12.2 (DMG CH_3); 29.5 (cyclohexene ring CH_2); 30.6 (cyclohexene ring CH_2); 33.8 (cyclohexene ring CH_2); 52.5 (OCH_3); 63.3 (cyclohexene ring C(NPhth)(CO_2CH_3); 121.8 (olefinic *C*H); 122.8 (aromatic *C*); 125.1 (*C*-3 py); 131.7 (aromatic C); 133.8 (aromatic *C*); 137.4 (*C*-4 py); 149.6 (DMG *C*=N); 150.0 (DMG *C*=N); 150.1 (*C*-2 py); 168.1 (Pht *C*=O); 173.0 (CO_2CH_3); *C*Co quaternary resonance not seen. FAB-MS (*m/z*, %) 653 (MH^+, 8%), 574 (MH^+-py, 29%). IR (cm^{-1}): 3452 (br, str.), 1742 (ester C=O str), 1711 (Pht C=O str.), 1371 (str.), 1233 (str.), 1089 (str.).

Microanalysis: Calcd for $C_{29}H_{33}N_6O_8Co{\cdot}H_2O$: C, 51.94; H, 5.26 N, 12.53. Found: C, 52.25; H, 4.98; N, 12.61.

3.3.3. [(1,4-Diacetyl-2,5-dioxo-1,4-diazaspiro[5.5]undec-8-en-9-yl)pyridinebis (dimethylglyoximato)]cobalt(III) hydrate (5a). Chromatography: ethyl acetate, R_f 0.38, isolated as an orange solid. Mp 215°C dec. ^{1}H NMR (CD_2Cl_2): δ 1.58 (br s, 2H, lattice water); 1.82 (m, 1H, cyclohexene ring proton); 2.00–2.40 (m, 4H, cyclohexene ring protons); 2.06 (s, 6H, DMG methyl protons); 2.07 (s, 6H, DMG methyl protons); 2.34 (s, 3H, NCOCH_3); 2.44 (s, 3H, NCOCH_3); 2.60 (d, 1H, J=16 Hz, cyclohexene ring proton); 2.73 (d, 1H, J=16 Hz, cyclohexene ring proton); 4.18 (d, 1H, J=19 Hz, piperazinedione CH_aH$_b$); 4.61 (d, 1H, J=19 Hz, piperazinedione CH$_a$$H_b$); 5.05 (dd, 1H, J=3 and 4.5 Hz, olefinic proton); 7.30 (m, 2H, H-3 py); 7.72 (m, 1H, H-4 py); 8.62 (m, 2H, H-2 py). ^{13}C NMR (CD_2Cl_2): δ 12.2 (DMG CH$_3$); 27.2 (NCOCH$_3$); 29.5 (NCOCH$_3$); 30.5 (cyclohexene ring CH$_2$); 32.3 (cyclohexene ring CH$_2$); 32.8 (cyclohexene ring CH$_2$); 46.8 (piperazinedione CH$_2$); 65.1 (spiro ring junction carbon); 120.6 (olefinic CH); 125.5 (C-3 py); 137.9 (C-4 py); 150.3 (C-2 py); 150.4 (dimethylglyoxime C=N); 167.4 (COCH$_3$); 169.0 (COCH$_3$); 171.9 (piperazinedione C=O); 177.8 (piperazinedione C=O); CCo quaternary resonance not seen. FAB-MS: (*m*/*z*, %) 632 (MH$^+$, 65%), 552 (M$^+$−py, 100%). IR (cm^{-1}): 3430 (med.), 1716 (acyclic amide C=O, str.), 1690 (cyclic amide C=O, str.), 1561 (med.), 1446 (med.), 1232 (str.), 1194 (str.), 1088 (med.). Microanalysis: Calcd for $C_{26}H_{34}N_7O_8Co.H_2O$: C, 48.08; H, 5.59; N, 15.09. Found: C, 48.69; H, 5.48 N, 15.04.

3.3.4. [(4-Acetyl-2,5-dioxo-1,4-diazaspiro[5.5]undec-8-en-9-yl) pyridinebis(dimethylglyoximato)] cobalt(III) (5b). Chromatography: 1:1 ethyl acetate/petroleum spirits, R_f 0.44, isolated as an orange solid. Mp 220°C dec. ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 1H, cyclohexene ring proton); 1.90 (m, 1H, cyclohexene ring proton); 2.00–2.15 (m, 2H, cyclohexene ring proton); 2.10 (s, 6H, DMG methyl protons); 2.11 (s, 6H, DMG methyl protons); 2.31 (m, 1H, cyclohexene ring proton); 2.50 (s, 3H, NCOCH_3); 2.87 (m, 1H, cyclohexene ring proton); 4.05 (d, 1H, J=18 Hz piperazinedione CH_aH$_b$); 4.47 (d, 1H, J=18 Hz, piperazinedione CH$_a$$H_b$); 5.18 (dd, 1H, J=2 and 4 Hz, olefinic proton); 5.75 (br s, 1H, NH); 7.32 (m, 2H, H-3 py); 7.73 (m, 1H, H-4 py); 8.61 (m, 2H, H-2 py). ^{13}C NMR ($CDCl_3$): δ 12.3 (DMG CH$_3$); 27.3 (NCOCH$_3$); 28.0 (cyclohexene ring CH$_2$); 32.7 (cyclohexene ring CH$_2$); 36.4 (cyclohexene ring CH$_2$); 45.9 (piperazinedione CH$_2$); 58.0 (spiro ring junction carbon); 119.6 (olefinic CH); 125.3 (C-3 py); 137.8 (C-4 py); 149.9 (C-2 py); 150.5 (dimethylglyoxime C=N); 165.4 (NCOCH$_3$); 171.5 (piperazinedione C=O); 172.4 (piperazinedione C=O); CCo quaternary resonance not seen. FAB-MS: (*m*/*z*, %) 590 (MH$^+$, 16%), 510 (MH$^+$−py, 97%). IR (cm^{-1}): 3452 (br., med.), 1727 (acyclic amide C=O, med.), 1698 (cyclic amide C=O, str.) 1682 (cyclic amide C=O, str.), 1560 (med.), 1447 (med.), 1369 (med.), 1266 (med.), 1218 (str.), 1088 (med.), 1038 (med.).

3.3.5. [(4-Acetyl-2,5-dioxo-3-methyl-1,4-diazaspiro[5.5]-undec-8-en-9-yl)pyridinebis (dimethylglyoximato)] cobalt(III) hydrate (5c). Chromatography: 19:1 ethyl acetate/MeOH, R_f=0.5, isolated as an orange solid. Mp>300°C dec. ^{1}H NMR ($CDCl_3$): δ 1.48 (d, J=7 Hz, 3H, CHCH_3); 1.76 (m, 1H, cyclohexene ring proton); 2.04–2.25 (m, 3H, cyclohexene ring protons); 2.16 (s, 12H, DMG methyl protons); 2.38 (m, 1H, cyclohexene ring proton); 2.50 (s, 3H, NC(=O)CH_3); 3.01 (br d, 1H, cyclohexene ring proton); 4.89 (q, J=8 Hz, 1H, CHCH$_3$); 5.21 (m, 1H, olefinic cyclohexene ring proton); 5.75 (br s, 1H, NH); 7.25 (m, 2H, H-3 py); 7.67 (m, 1H, H-4 py); 8.54 (m, 2H, H-2 py). ^{13}C NMR ($CDCl_3$): δ 12.2 (DMG CH$_3$); 20.0 (CHCH$_3$); 27.3 (NCOCH$_3$); 28.0 (cyclohexene ring CH$_2$); 34.9 (cyclohexene ring CH$_2$); 38.3 (cyclohexene ring CH$_2$); 53.17 (CHCH$_3$); 58.27 (spiro carbon); 119.9 (olefinic carbon); 125.3 (C-3 py); 137.7 (C-4 py); 149.9 (C-2 py); 150.2 (dimethylglyoxime C=N); 150.4 (dimethylglyoxime C=N); 168.2 (C=O); 172.2 (C=O); 172.6 (C=O). FAB-MS: (*m*/*z*, %) 604 (MH$^+$, 21%), 603 (M$^+$, 14%), 525 (MH$^+$−py, 100%), 524 (M$^+$−py, 95%). IR (cm^{-1}): 3370 (br., med), 1692 (C=O, str.), 1563 (med.), 1445 (med.), 1373 (str.), 1228 (str.), 1090 (str.), 1037 (str.). Microanalysis: Calcd for $C_{25}H_{34}N_7O_7Co{\cdot}H_2O$: C, 48.31; H, 5.84; N, 15.78. Found: C, 48.16; H, 5.64; N, 15.63.

3.3.6. [(1,4-Diacetyl-2,5-dioxo-3-methyl-1,4-diazaspiro-[5.5]undec-8-en-9-yl)pyridinebis (dimethylglyoximato)] cobalt(III) (5d). Chromatography: ethyl acetate, R_f=0.3, isolated as an orange solid. Mp>300°C (dec.). ^{1}H NMR ($CDCl_3$): δ 1.53 (d, J=7 Hz, 3H, CHCH_3); 1.61 (m, 1H, cyclohexene ring proton); 2.0–2.5 (m, 4H, cyclohexene ring protons); 2.13 (s, 6H, DMG methyl protons); 2.14 (s, 6H, DMG methyl protons); 2.37 (s, 3H, NC(=O)CH_3); 2.43 (s, 3H, NC(=O)CH_3); 2.67 (br m, 1H, cyclohexene ring proton); 5.00 (q, 1H, CHCH$_3$); 5.14 (m, 1H, olefinic cyclohexene ring proton); 7.31 (m, 2H, H-3 py); 7.72 (m, 1H, H-4 py); 8.64 (m, 2H, H-2 py). FAB-MS: (*m*/*z*, %) 646 (MH$^+$, 17%), 566 (MH$^+$−py, 40%). IR (cm^{-1}): 3434 (br., med), 1707 (C=O, str.), 1689 (str.), 1563 (med.), 1448 (med.), 1365 (med.), 1230 (str.), 1088 (str.), 1037 (str.). Microanalysis: Calcd for $C_{27}H_{36}N_7O_8Co$: C, 50.24; H, 5.62; N, 15.19. Found: C, 49.60; H, 5.92; N, 15.24.

3.4. General procedure for I_2 cleavage reactions

To a solution of the cobalt cycloadduct in dichloromethane (10 mL per 0.1 mmol of Co cycloadduct) at 0°C and stirring under N_2 was added I_2 (1.1 equiv. in 3 mL of dichloromethane). The reaction mixture was allowed to warm slowly to room temperature while stirring under N_2 and the progress of the reaction was monitored by TLC for the disappearance of starting material. Upon completion of the reaction, the reaction mixture was washed once with 10% $Na_2S_2O_3$ solution (10 mL per 0.1 mmol of Co cycloadduct), followed by water (10 mL). The organic phase was then dried and the solvent removed under reduced pressure. The resulting residue was purified by column or radial chromatography using a suitable eluent as determined by TLC analysis.

3.4.1. 4-Iodo-1-trifluoroacetylamino-cyclohex-3-ene-carboxylic acid methyl ester (6a). The title compound is not stable to chromatography and was purified rapidly via radial chromatography. TLC: 6:1 petroleum spirit/ethyl

acetate, R_f=0.37, isolated as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.00–2.80 (m, 6H, cyclohexene ring protons); 3.77 (s, 3H, CO_2CH_3); 6.26 (m, 1H, olefinic *H*); 6.44 (s, 1H, N*H*). MS: (*m*/*z*, %) 378 (MH^+, 0.3%), 318 ($M^+-CO_2CH_3$), 264 ($M^+-NCO_2CF_3-CO_2Me$, 20%), 137 (34%). HRMS: Calcd for $C_{13}H_{13}F_3INO_3$ 377.9814 Found 377.9811.

3.4.2. 1-(1′,3′-Dioxo-1′,3′-dihydroisoindol-2′-yl)-4-iodocyclohex-3-enecarboxylic acid methyl ester (6b). Chromatography: 2:1 petroleum spirit/ethyl acetate, R_f=0.6, isolated as a white solid. Mp 95–97°C. Yield: 88%. ^{1}H NMR ($CDCl_3$): δ 2.35 (m, 1H, cyclohexene ring proton); 2.55 (m, 2H, cyclohexene ring protons); 2.72 (m, 1H, cyclohexene ring proton); 2.98 (m, 1H, cyclohexene ring proton); 3.32 (m, 1H, cyclohexene ring proton); 3.75 (s, 3H, CO_2CH_3); 6.36 (m, 1H, olefinic proton); 7.72–7.84 (m, 4H, aromatic ring protons). ^{13}C NMR ($CDCl_3$): δ 30.6 (cyclohexene ring CH_2); 35.0 (cyclohexene ring CH_2); 36.1 (cyclohexene ring CH_2); 53.0 (CO_2CH_3); 61.0 (spiro carbon); 93.0 (olefinic *C*H); 123.3 (aromatic *C*); 131.5 (aromatic *C* or olefinic *C*–I); 134.2 (aromatic *C*); 168.4 (Pht *C*=O); 172.0 (CO_2CH_3); one quaternary resonance (either aromatic *C* or olefinic *C*–I) not seen. EI-MS: (*m*/*z*, %) 411 (M^+, 0.5%), 352 ($M^+-CO_2CH_3$, 44%), 264 (MH^+−Pht, 100%), 148 (67%). HRMS: Calcd for $C_{16}H_{14}INO_4$ 410.9968. Found 410.9965. IR (cm^{-1}): 3444 (br., med.), 1729 (ester C=O, med.), 1714 (Pht C=O, str.), 1373 (med.), 718 (med.). Microanalysis: Calcd for $C_{16}H_{14}INO_4$: C, 46.74; H, 3.43; N, 3.41. Found C, 47.15; H, 3.53; N, 3.34.

3.4.3. 1,4-Diacetyl-9-iodo-1,4-diazaspiro[5.5]undec-8-ene-2,5-dione (6c). Chromatography: 100% ethyl acetate, R_f=0.84, isolated as a solid. Yield: 65%. ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 1H, cyclohexene ring proton); 2.00–2.80 (m, 4H, cyclohexene ring protons); 2.48 (s, 3H, NCOCH_3); 2.59 (s, 3H, NCOCH_3); 2.90 (m, 1H, cyclohexene ring proton); 4.22 (d, 1H, *J*=19 Hz, piperazinedione CH_aH$_b$); 4.80 (d, 1H, *J*=19 Hz, piperazinedione CH$_a$$H_b$); 6.28 (m, 1H, olefinic proton). MS: (*m*/*z*, %) 390 (M^+, 18%), 348 (MH^+−Ac, 75%), 288 (35%), 232 (100%), 221 (MH^+−Ac–I, 75%), 179 (65%), 159 (47%). HRMS: Calcd for $C_{13}H_{15}IN_2O_4$ 390.0077 Found 390.0079. IR (cm^{-1}): 3432 (br., str.), 1719 (acyclic amide C=O, str.), 1702 (acyclic amide C=O, str.), 1680 (cyclic amide C=O, str.), 1366 (med.), 1263 (med.), 1234 (med.), 1204 (med.).

3.4.4. 4-Acetyl-9-iodo-1,4-diazaspiro[5.5]undec-8-ene-2,5-dione (6d). Chromatography: 1:1 petroleum spirit/ethyl acetate, R_f=0.44, isolated as a white solid. Yield: 64%. Mp 185–187°C. ^{1}H NMR ($CDCl_3$): δ 1.89 (m, 1H, cyclohexene ring proton); 2.22 (m, 2H, cyclohexene ring proton); 2.59 (s, 3H, NCOCH_3); 2.62–2.82 (m, 2H, cyclohexene ring protons); 3.05 (m, 1H, cyclohexene ring proton); 4.20 (d, 1H, *J*=18 Hz, piperazinedione CH_aH$_b$); 4.64 (d, 1H, *J*=18 Hz, piperazinedione CH$_a$$H_b$); 6.24 (br s, 1H, N*H*); 6.34 (m, 1H, olefinic proton). ^{13}C NMR ($CDCl_3$): δ 27.3 (CO*C*H$_3$); 32.9 (cyclohexene ring CH_2); 34.6 (cyclohexene ring CH_2); 37.7 (cyclohexene ring CH_2); 46.0 (piperazinedione CH_2); 56.5 (spiro ring junction carbon); 93.8 (olefinic *C*H); 132.3 (olefinic *C*–I); 165.6 (N*C*OCH$_3$); 170.5 (piperazinedione *C*=O); 172.1 (piperazinedione *C*=O). MS: (*m*/*z*, %) 348 (M^+, 50%), 306 (MH^+−Ac, 29%), 221 (M^+−I, 100%), 179 (MH^+−I–Ac, 10%). HRMS: Calcd for $C_{11}H_{13}IN_2O_3$ 347.9971 Found 347.9969. IR (cm^{-1}): 3449 (br, str.), 1711 (acyclic amide C=O, str.), 1707 (acyclic amide C=O, str.), 1679 (cyclic amide C=O, str.), 1412 (med.), 1368 (med.), 1266 (med.), 1253 (med.), 1221 (med.), 1205 (med.). Microanalysis: Calcd for $C_{11}H_{13}IN_2O_3$: C, 37.95; H,.3.76; N, 8.05. Found: C, 37.86; H, 3.63; N, 7.89.

3.4.5. 4-Acetyl-9-iodo-3-methyl-1,4-diaza-spiro[5.5]undec-8-ene-2,5-dione (6e). Chromatography: 2:1 petroleum spirit/ethyl acetate, R_f=0.22, isolated as a white solid. Yield: 62%. Mp 97–100°C. ^{1}H NMR ($CDCl_3$): δ 1.58 (d, *J*=7 Hz, 3H, CHCH_3), 1.94 (m, 1H, cyclohexene ring proton), 2.20–2.30 (m, 2H, cyclohexene ring protons), 2.55 (s, 3H, C(=O)CH_3), 2.73 (d, *J*=5 Hz, 2H, cyclohexene ring protons), 3.10 (m, 1H, cyclohexene ring proton), 4.98 (q, *J*=7 Hz, 1H, C*H*CH$_3$), 6.36 (m, 1H, IC=C*H*), 7.12 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 20.25 (CH*C*H$_3$), 27.45 (C(=O)*C*H$_3$), 34.60 (cyclohexene ring carbon), 35.10 (cyclohexene ring carbon), 39.35 (cyclohexene ring carbon), 53.11 (*C*HCH$_3$), 56.80 (spiro carbon), 93.80 (olefinic =*C*H), 132.46 (olefinic =*C*I), 168.8 (*C*=O), 171.1 (*C*=O), 171.99 (*C*=O). MS: (*m*/*z*, %) 362 (M^+, 37%), 320 (M^+−Ac, 27%), 235 (55%), 193 (62%), 140 (31%). HRMS Calcd for $C_{12}H_{15}IN_2O_3$ 362.0127. Found 362.0127. IR (cm^{-1}): 1710 (acyclic amide C=O, str.), 1674 (cyclic amide C=O, str.), 1424 (med.), 1368 (str.), 1255 (str.), 1237 (str.), 1221 (str.), 1111 (str.), 1036 (str.). $[\alpha]_D^{20}$=+76 (1 mg/mL, CH_2Cl_2).

3.5. Other methods of cleavage

3.5.1. 1-(1′,3′-Dioxo-1′,3′-dihydroisoindol-2′-yl)-cyclohex-3-enecarboxylic acid methyl ester (7). (a) *Via photolysis of cycloadduct* **4d**

Cobalt cycloadduct **4d** (80 mg, 0.12 mmol) was dissolved in degassed dichloromethane (24 mL) and photolysed under N_2 atmosphere (N_2 balloon) with a medium-pressure mercury vapour lamp (125 W) in a water-cooled quartz jacket. The progress of the reaction was monitored by TLC for the disappearance of starting cycloadduct. Upon completion of the reaction or when no further reaction was noted, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified using column chromatography (1:1 ethyl acetate/petroleum spirits, R_f 0.8) to leave **7** as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.07 (m, 2H, cyclohexene ring proton); 2.24 (m, 1H, cyclohexene ring proton); 2.65 (m, 1H, cyclohexene ring proton); 2.97 (m, 1H, cyclohexene ring proton); 3.21 (m, 1H, cyclohexene ring proton); 3.74 (s, 3H, CO_2CH_3); 5.72 (m, 1H, olefinic proton); 5.75 (m, 1H, olefinic proton); 7.68–7.82 (m, 4H, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 22.3 (cyclohexene ring CH_2); 28.0 (cyclohexene ring CH_2); 31.7 (cyclohexene ring CH_2); 52.8 (CO_2CH_3); 62.6 (spiro carbon); 123.1 (aromatic *C*); 124.5 (olefinic *C*); 125.4 (olefinic *C*); 131.7 (aromatic *C*); 134.1 (aromatic *C*); 168.6 (Pht *C*=O); 172.6 (CO_2CH_3). MS: (*m*/*z*, %) 285 (M^+,4%), 253 (MH^+−OMe, 15%), 225 ($MH^+-CO_2CH_3$, 30%), 148 (62%), 138 (100%), 104 (35%), 79 (40%). HRMS: Calcd for $C_{16}H_{15}NO_4$ 285.1001. Found 285.0999.

(b) *Via reductive cleavage of cycloadduct* **4d** *with dithiothreitol*

To a solution of cycloadduct **4d** (60 mg, 0.092 mmol) in degassed dichloromethane (2 mL) was added dithiothreitol (15.6 mg, 0.10 mmol) under N_2 atmosphere. The reaction mixture was refluxed under N_2 and the progress of the reaction was monitored by TLC for the disappearance of starting material. Upon completion of the reaction or when no further reaction was noted, the solvent was removed under reduced pressure and the resulting residue purified using column chromatography (1:1 ethyl acetate/petroleum spirits, R_f 0.8). A white solid was isolated (12 mg, 44%) which was found to be identical to **7** by spectroscopic comparison.

3.5.2. Cleavage of cycloadduct 4d with Br_2 [1-(1′,3′-dioxo-1′,3′-dihydroisoindol-2′-yl)-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (8)]. To a stirred solution of cycloadduct **4d** (43 mg, 0.066 mmol) in dichloromethane at 0°C and under N_2 was added 1.1 equiv. of Br_2 (0.11 mL of a 0.66 M solution in dichloromethane). The reaction mixture was allowed to warm slowly to room temperature while stirring under N_2 and the progress of the reaction was monitored by TLC for the disappearance of starting material. Upon completion of the reaction, saturated $NaHCO_3$ solution (4.5 mL) was added and the resulting mixture stirred for 5 min. The organic phase was separated, then dried and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (2:1 ethyl acetate/petroleum spirits, R_f 0.4) to leave **8** as a white solid (8.4 mg, 42%). Mp 115–118°C. ^{1}H NMR ($CDCl_3$): δ 2.50–2.71 (m, 2H, cyclohexanone ring protons); 2.80–3.05 (m, 2H, cyclohexanone ring protons); 3.81 (s, 3H, CO_2CH_3); 6.19 (d, 1H, J=10 Hz, olefinic proton β to ketone); 7.16 (d, 1H, J=10 Hz, olefinic proton α to ketone); 7.70–7.90 (m, 4H, aromatic protons). ^{13}C NMR ($CDCl_3$): δ 30.1 (cyclohexanone ring CH_2); 34.4 (cyclohexanone ring CH_2); 53.4 (CO_2CH_3); 60.6 (spiro carbon); 123.6 (aromatic *C*); 130.1 (olefinic *C* β to ketone); 131.4 (aromatic *C*); 134.6 (aromatic *C*H); 145.1 (olefinic *C* α to ketone); 167.5 (Pht *C*=O); 168.6 (CO_2CH_3); 197.0 (cyclohexanone ring *C*=O). MS: (*m*/*z*, %) 299 (M^+, 10%), 267 (M^+-32, 11%), 240 ($M^+-CO_2CH_3$, 100%), 212 (66%), 152 ($PhtH^+$, 65%). HRMS: Calcd for $C_{16}H_{13}NO_5$ 299.0794. Found 299.0788. IR (cm^{-1}): 1731 (C=O, str.), 1707 (C=O, str.), 1678 (C=O, str.), 1375 (str.), 1262 (med.), 1170 (med.), 1132 (str.), 713 (str.).

Acknowledgements

We thank the Australian Research Council for financial support and P. B. Huleatt and B. A. Burkett for their assistance.

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