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Indium-Mediated Selective Introduction of a 1,3-Butadien-2-yl Group at the C4-Position in 2-Azetidinones and Application of 1,3-Diene-Tethered 2-Azetidinones in the Diels–Alder Reaction

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Abstract: The reaction of 4-acetoxy-2-azetidinones with organoindium reagents generated in situ from indium and 1,4-dibromo-2-butyne in the presence of LiCl in DMF selectively produced 2-azetidinones which contain a 1,3-butadienyl-2-yl group at the C4-position in good yields. The Diels–Alder reaction of 4-[(1-methylene)prop-2-enyl]-2-azetidinones with a variety of dienophiles provided 2-azetidinones with valuable functional-group-substituted six-membered rings at the C4-position in good yields.

Keywords: 1,3-butadien-2-ylation · azetidinones · catalysis · Diels–Alder reactions · indium

Introduction

β-Lactam antibiotics, which are a large class of antibiotics characterized by the presence of a 2-azetidinone ring, proved to be therapeutic agents of unique effectiveness, conjugating a broad spectrum of activity with low toxicity.[1] Therefore, introduction or transformation of functional groups on the ring of 2-azetidinone, which is the core of the biological activity, represents one of the most important endeavors in β-lactam chemistry.[2] Although introduction of various heteroatoms, such as oxygen, halide, and nitrogen at the C4-position of 2-azetidinone have been reported, the selective introduction of carbon nucleophiles such as ethynyl,[3] allyl,[4] vinyl,[4a,b] propargyl,[5] and allenyl[6] groups is a mostly attractive and fundamental problem in the field of carbapenem syntheses because further functionalization of these groups has high possibilities for the construction of the bicyclic nucleus.[7] Generally, it has been accomplished as a result of the ability of 4-acetoxy-2-azetidinone to take part in S_N1 reactions very easily at the C4-position via acyliminium or acylimine intermediates.[8] Therefore, a lot of effort has been devoted to the selective introduction of these groups by the reaction of 4-acetoxy-2-azetidinones with a variety of organometallic nucleophiles.[2b] However, introduction of a 1,3-butadien-2-yl and 1,3-butadien-1-yl group on the 2-azetidinone ring has remained a formidable challenge due to the tremendous further functionalization through the Diels–Alder reactions. Recently, the selective indium-mediated 1,3-butadien-2-ylation at the C3-position of azetidine-2,3-dione was reported by Alcaide et al.[9] Although 1,3-butadien-1-ylation at the C4-position of 2-azetidinone from the reaction of allylsilane with 4-oxoazetidine-2-carbaldehyde followed by dehydration,[10] [3,3]-Sigmatropic rearrangements in α-allenic methanesulfonates,[11] and [2+2] cycloaddition of butadienylketene with various imines[12] have been found, there is no synthetic method for the direct introduction of the 1,3-butadien-2-yl group at the C4-position of 2-azetidinone through substitution reactions from 4-acetoxy-2-azetidinone.[13] Accordingly, we envisioned the introduction of the 1,3-butadien-2-yl group at the C4-position of 2-azetidinone because 2-azetidinone, which has this group, could be further functionalized through Diels–Alder reactions to produce 2-azetidinones possessing various six-membered rings at the C4-position. Described herein is a selective introduction of a 1,3-butadien-2-yl group on the C4-position of 2-azetidinone with organoindium reagents generated in situ from 1,4-dibromo-2-butyne (**3**) and indium as well as the Diels–Alder reaction of 4-[(1-methylene)prop-2-enyl]-2-azetidinones with a variety of dienophiles (Scheme 1).

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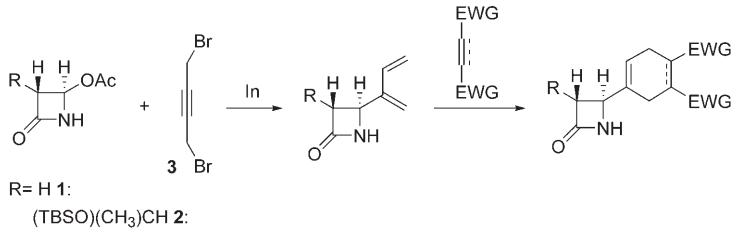
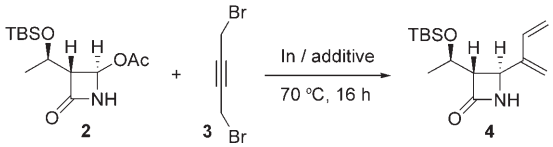


Scheme 1. 1,3-Buadien-2-ylation of 4-acetoxy-2-azetidinones and their application to the Diels–Alder reaction.

Results and Discussion

In our initial study, optimum conditions for the introduction of an indium-mediated 1,3-butadien-2-yl group at the C4-position of 2-azetidinones were examined by the reaction of [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone **2** with organoindium reagents generated in situ from indium and 1,4-dibromo-2-butyne (**3**) (Table 1). Reaction of **2** with 1.5 equivalents of **3** and 3.0 equivalents of indium did not proceed in the presence of KI as an additive in THF (entry 1). However, treatment of **2** with 3.0 equivalents of **3**, 2.0 equivalents of indium, and 3.0 equivalents of KI selectively gave rise to the desired product **4** in 62% yield (entry 5). No other isomeric products, especially in regard to the 1,3-butadienyl group, were obtained in this reaction. Product yields were dependent on the concentration of the reaction mixture (entries 3–6).

Table 1. Reaction optimization.[a]

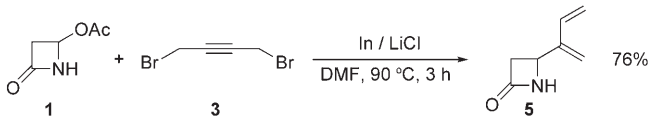


Entry	In [equiv]	**3** [equiv]	Additive	Solvent	Yield [%][b]
1	3.0	1.5	KI	THF[c]	0
2	2.0	4.0	KI	THF[c]	40
3	2.0	3.0	KI	THF[c]	43
4	2.0	3.0	KI	THF[d]	51
5	2.0	3.0	KI	THF	62
6	2.0	3.0	KI	THF[e]	29
7	2.0	3.0	KI[f]	THF	49
8	2.0	3.0	–	THF	48
9	3.0	2.5	KI	THF	68
10	6.0	2.5	KI	H_2O	0[g,h]
11	2.0	2.5	KI	H_2O/THF[i]	0[h]
12	3.0	2.5	KI	CH_3CN	20
13	3.0	2.5	LiBr	THF	46
14	3.0	2.5	LiI	THF	58
15	3.0	2.5	LiCl	THF	73
16	3.0	2.5	LiCl	DMF	77[g,j]
17	3.0	2.5	KI	DMF	66[k]

[a] Reactions were performed in the presence of additive (3 equiv) in THF (2 mL). [b] Isolated yield. [c] THF (5 mL) was used. [d] THF (3 mL) was used. [e] THF (1.5 mL) was used. [f] KI (2 equiv) was used. [g] Reaction was heated at 90 °C. [h] Reaction time was 24 h. [i] H_2O/THF 1:1. [j] Reaction time was 3 h. [k] 100 °C for 3 h.

Among several reaction conditions that were examined, the best results were obtained with the organoindium reagent, which was generated in situ from the reaction of 3.0 equivalents of indium with 2.5 equivalents of **3** in the presence of 3.0 equivalents of LiCl, producing **4** in 77% yield (DMF, 90 °C, 3 h, entry 16). The use of indium in less than 3.0 equivalents and 1,4-dibromo-2-butyne in less than 2.5 equivalents resulted in a sluggish reaction and gave lower yields as well as a longer reaction time, indicating that the stoichiometry of indium and **3** is critically important for successful reactions. The use of lithium chloride as an additive is very essential for good results (entries 9 and 13–17). DMF was the best solvent among several reaction media (DMF, THF, H_2O, H_2O/THF, CH_3CN) that were screened.

Encouraged by these results, we next examined the reaction of 4-acetoxy-2-azetidinone (**1**) with an organoindium reagent generated in situ from indium and **3** under the optimum conditions, producing 4-[(1-methylene)prop-2-enyl]-2-azetidinone (**5**) in 76% yield (Scheme 2).

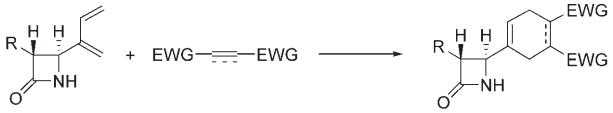


Scheme 2. Reaction of 4-acetoxy-2-azetidinone with organoindium reagents.

To establish the synthetic potential of 1,3-diene-tethered 2-azetidinones, the Diels–Alder reactions of **4** and **5** with a variety of dienophiles were examined (Table 2). Treatment of **5** with 2.0 equivalents of **6e** gave the desired adduct **7e** in 88% yield (dr = 1:1.6) in toluene at 110 °C for 48 h (entry 6). However, **7e** was produced in a quantitative yield (dr = 1:1.6) in acetonitrile (25 °C, 24 h) in the presence of 5 mol% $InCl_3$ (entry 5). Exposure of **5** to maleimide (**6d**) afforded **7d** in 72% yield under these conditions (entry 4).[14] Similarly, the reaction of **5** with a variety of dienophiles, such as tetra(cyano)ethylene (**6a**), dimethylacetylene dicarboxylate (DMAD, **6b**), and dimethyl fumarate (**6c**), gave rise to the desired adducts in the presence of 5 mol% $InCl_3$ in good to excellent yields (CH_3CN, 25 °C; entries 1–3).

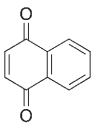
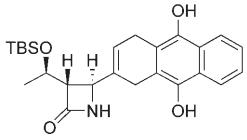
Next, we turned our attention to the Diels–Alder reaction of **4** with various dienophiles. Reaction of **4** with tetra(cyano)ethylene and DMAD afforded **7f** and **7g** in 86 and 83% yields, respectively, in benzene at 83 °C (entries 7 and 8). Treatment of **4** with 4.0 equivalents of dimethyl fumarate (**6c**) and dimethyl maleate (**6f**) furnished the Diels–Alder adducts **7h** (dr = 1:1.5) and **7i** (dr = 1:1.9) in 96 and 95% yields, respectively (entries 9 and 10). Compound **4** reacted with maleimide (**6d**) to afford **7j** in a quantitative

Table 2. Diels–Alder reaction of 1,3-diene-tethered 2-azetidinones with dienophiles.[a]



Entry	Diene	Dienophile	T [°C]	t [h]	Product	Yield [%][b]
1	**5**	**6a**	25	24	**7a**	85[c]
2	**5**	**6b**	25	48	**7b**	83[c]
3	**5**	**6c**	25	24	**7c**	72[c,d]
4	**5**	**6d**	25	24	**7d**	72[c]
5	**5**	**6e**	25	24	**7e**	98[c,e]
6	**5**		110	48		88[e,f]
7	**4**	**6a**	83	5	**7f**	86[g]
8	**4**	**6b**	83	48	**7g**	83[g]
9	**4**	**6c**	83	48	**7h**	96[d,g,h]
10	**4**	**6f**	83	48	**7i**	95[d,g,i]
11	**4**	**6d**	83	24	**7j**	99[g]
12	**4**	**6g**	25	24	**7k**	93[c]
13	**4**		110	48		83[e]
14	**4**	**6e**	110	48	**7l**	89[e]
15	**4**		25	48		98[c]
16	**4**		25	48		56[j]

Table 2. (Continued)

Entry	Diene	Dienophile	T [°C]	t [h]	Product	Yield [%][b]
17	**4**	 **6h**	83	48	 **7m**	84[g]

[a] Dienophiles (2 equiv) were used. [b] Isolated yield. [c] CH_3CH was used as a solvent in the presence of 5 mol% of $InCl_3$. [d] Dienophile (4.0 equiv) was used. [e] Diastereomeric ratio = 1:1.6. [f] Toluene was used as a solvent. [g] Benzene was used as a solvent. [h] Diastereomeric ratio 1:1.5. See reference [14]. [i] Diastereomeric ratio = 1:1.9. [j] DMF was used as a solvent and 5 mol% of $InCl_3$ was used.

yield in benzene (83 °C, 24 h, entry 11). Reaction of **4** with *N*-ethyl maleimide (**6g**) gave **7k** in 83% yield (toluene, 110 °C, 48 h, entry 13). However, the use of 5 mol% of $InCl_3$ in acetonitrile accelerated the Diels–Alder reaction, producing **7k** in 93% yield (entry 12). Refluxing **4** and **6e** in toluene (110 °C, 48 h) afforded the desired cycloadduct **7l** in 89% yield (entry 14). Although compound **4** reacted with **6e** to give the desired adduct **7l** in 56% yield in the presence of 5 mol% of $InCl_3$ (DMF, 25 °C, 48 h, entry 16), the use of acetonitrile gave **7l** in a quantitative yield (entry 15). Compound **7l** as a representative was characterized structurally by using X-ray crystallography (Figure 1).[15] As shown in entry 17, the Diels–Alder reaction with concomitant aromatization proceeded by treating **4** with 1,4-naphthoquinone, affording cycloadduct **7m** in 84% yield (benzene, 83 °C, 48 h).

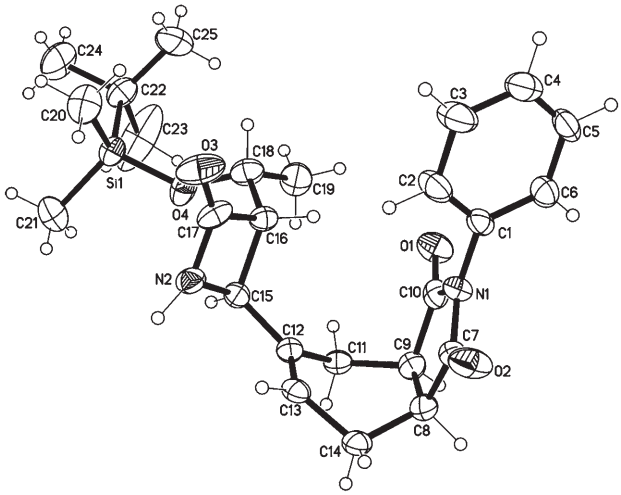
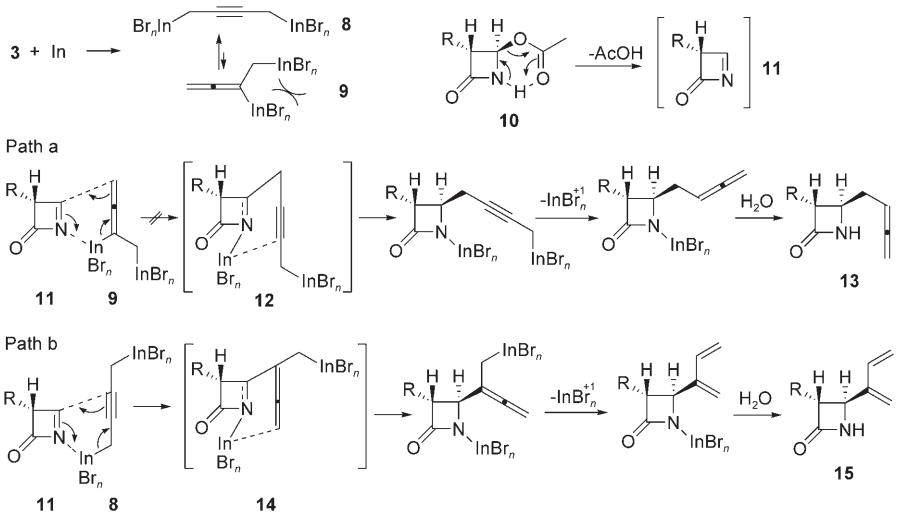


Figure 1. Projection of a molecule of compound **7l** as determined by X-ray crystallography.

Although the mechanism for the indium-mediated 1,3-butadien-2-ylation of 4-acetoxy-2-azetidinones by using 1,4-dibromo-2-butyne has not been established, a possible reaction pathway is described in Scheme 3.[16,9b] It may be reasonable to postulate a metallotropic rearrangement between the propargylindium (**8**) and allenylindium (**9**) reagents generated in situ from indium and 1,4-dibromo-2-butyne. The reactions of **8** and **9** with 4-acetoxy-2-azetidinones have trouble with competing reactions. Thus, both intermediates from this equilibrium between **8** and **9** can react with the acylimines **11** obtained through the elimination of AcOH from 4-acetoxy-2-azetidinones **10**, producing 4-(2,3-butadien-1-yl)-2-azetidinone **13** or 4-[(1-methylene)prop-2-enyl]-2-azetidinone **15**. The formation of 2-azetidinones (**13** and **15**) is consistent with participation of the six-membered cyclic transition structures **12** (path a) and **14** (path b), respectively. It seems feasible to suggest that the regiochemical preference observed for the indium-promoted reactions of 1,4-dibromo-2-butyne with 4-acetoxy-2-azetidinones must be controlled by steric effects. The isomerization of propargylindium to allenylindium is presumably prohibited by the steric effect of both $InBr_n$ substituents. Thus, the propargylindium reagent **8**



Scheme 3. Plausible mechanism for the regioselective synthesis of 4-[(1-methylene)prop-2-enyl]-2-azetidinone.

undergoes nucleophilic addition to the acylimine **11** to afford exclusively allenyl compounds **14**, which after protiodeindation provided 4-[(1-methylene)prop-2-enyl]-2-azetidinones **15** through path b (Scheme 3).

The stereochemistry of 1,3-diene-tethered 2-azetidinone at the C4-position for compounds **4** was assigned by analysis of the coupling constants in the NMR spectra. The stereoselectivity in the addition reaction of an organoindium reagent generated in situ from indium and **3** with 4-acetoxy-2-azetidinones **2** is believed to be controlled by the bulky 1-(*tert*-butyldimethylsilyloxy)ethyl group at the C3-position, in which one face of the iminyl group is blocked, thus the organoindium reagent is delivered to the less-hindered face.[15b]

Conclusion

We have shown that the reaction of 4-acetoxy-2-azetidinones with organoindium reagents generated in situ from indium and 1,4-dibromo-2-butyne in the presence of LiCl in DMF selectively produced 2-azetidinones which contained a 1,3-butadienyl-2-yl group at the C4-position in good yields. It was also demonstrated that the Diels–Alder reaction of 4-[(1-methylene)prop-2-enyl]-2-azetidinones with a variety of dienophiles provided 2-azetidinones possessing valuable functional-group-substituted six-membered rings at the C4-position in good yields; in this way, it serves as a new synthetic methodology for β-lactam compounds.

Experimental Section

General: Reactions were carried out in oven-dried glassware under a nitrogen atmosphere. All commercial reagents were used without purification and all solvents were reaction grade. THF was freshly distilled from sodium/benzophenone under a nitrogen atmosphere. All reaction mixtures were monitored by TLC using Merck silica gel $60F_{254}$ precoated glass plates, which were visualized with UV light, and then, developed by using Fluka silica gel 60 (0.040–0.063 mm, 230–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX FT (400 MHz) spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent ($\delta=7.24$ for ^{1}H and $\delta=77.0$ ppm for ^{13}C NMR spectra). IR spectra were recorded on a JASCO FTIR-460 plus FTIR spectrometer as either a thin film or as a solid suspended in a potassium bromide pellet. Indium metal (99.99%, 100 mesh), 4-acetoxy-2-azetidinone, and [3*R*(1′*R*,4*R*)]-(+)-4-acetoxy-3-[1′-(*tert*-butyldimethylsilyloxy)-ethyl]-2-azetidinone were purchased from Aldrich. 1,4-Dibromo-2-butyne was prepared from the reaction of 2-butyne-1,4-diol with PBr_3.[17] Commercially available solvents were purified by standard procedures.

3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-[(1-methylene)prop-2-enyl]-azetidin-2-one (4): Propargyl bromide (264.9 mg, 1.25 mmol) was added to a solution of indium (172.2 mg, 1.5 mmol) and lithium chloride (174.0 mg, 1.5 mmol) in DMF (1.5 mL) under a nitrogen atmosphere at room temperature. After the mixture had been stirred for 40 min, 4-acetoxy-2-azetidinone (143.7 mg, 0.5 mmol) in DMF (0.5 mL) was added to the reaction mixture. After further stirring at 90 °C for 3 h, the mixture was poured into saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3×20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:1) to afford **4** (108.0 mg, 77%). M.p. 84 °C; $R_f=0.6$ (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=6.38$ (dd, $J=17.74$, 11.12 Hz, 1H), 5.84 (s, 1H), 5.46 (d, $J=17.72$ Hz, 1H), 5.25 (d, $J=9.69$ Hz, 2H), 5.18 (d, $J=11.12$ Hz, 1H), 4.48 (d, $J=1.40$ Hz, 1H), 4.29–4.23 (m, 1H), 2.95 (t, $J=5.31$ Hz, 1H), 1.22 (d, $J=6.40$ Hz, 3H), 0.89 (s, 9H), 0.09 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=168.8$, 145.2, 135.4, 115.3, 114.5, 66.0, 65.0, 50.3, 25.7, 22.8, 17.9, −4.3, −4.9 ppm; IR (film): $\tilde{\nu}=3176$, 2926, 1757, 776 cm^{-1}.

4-[(1-Methylene)prop-2-enyl]azetidin-2-one (5): Compound **5** was produced by a similar procedure to that described for the preparation of **4**. M.p. 83 °C; $R_f=0.4$ (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=6.41$ (dd, $J=17.94$, 11.07 Hz, 1H), 5.99 (s, 1H), 5.26 (s, 1H), 5.20 (s, 1H), 5.16 (dd, $J=17.81$, 3.84 Hz, 2H), 4.40 (s, 1H), 3.31 (ddd, $J=14.58$, 5.43, 2.41 Hz, 1H), 2.71 ppm (dd, $J=14.60$, 2.63 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=167.6$, 144.8, 135.8, 114.7, 114.6, 47.5, 45.7 ppm; IR (KBr): $\tilde{\nu}=1752$ cm^{-1}.

5-(4-Oxoazetidin-2-yl)-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7d): In a V-vial, a solution of **4** (36.9 mg, 0.3 mmol), maleimide (58.2 mg, 0.6 mmol), and indium trichloride (2.8 mg, 0.015 mmol) in CH_3CN (0.5 mL) was stirred at room temperature for 24 h. After this time, the reaction mixture was poured into saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3×20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:1) to afford **7d** (47.4 mg, 72%). $R_f=0.3$ (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta=12.88$ (s, 1H), 8.06 (s, 1H), 5.81 (t, $J=3.27$ Hz, 1H), 3.50 (d, $J=1.49$ Hz, 1H), 3.17 (d, $J=6.73$ Hz, 1H), 3.11 (d, $J=7.52$ Hz, 1H), 2.99 (dd, $J=14.58$, 5.29 Hz, 1H), 2.43 (d, $J=14.01$ Hz, 1H), 2.37–2.28 (m, 2H), 2.15 (dd, $J=14.90$, 7.51 Hz, 1H), 2.06 ppm (dd, $J=15.10$, 7.04 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta=181.72$, 181.70, 167.1, 139.6, 122.8, 49.6, 42.8, 23.7, 22.6 ppm; IR (film): $\tilde{\nu}=3418$, 2249, 1655, 1025, 1003, 763 cm^{-1}.

4-(4-Oxoazetidin-2-yl)cyclohex-4-ene-1,1,2,2-tetracarbonitrile (7a): Compound **7a** was prepared by a similar procedure to that described for **7d**. $R_f=0.3$ (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta=8.22$ (s, 1H), 5.88 (s, 1H), 4.14 (s, 1H), 3.49–3.30 (m, 4H), 3.13 (dd, $J=14.72$, 5.28 Hz, 1H), 2.64 ppm (d, $J=14.75$, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta=167.1$, 133.7, 117.0, 112.5, 112.4, 112.3, 112.32, 49.4, 44.1, 31.3, 30.3, 21.0, 14.1 ppm; IR (film): $\tilde{\nu}=3388$, 1759, 1165, 736 cm^{-1}.

4-(4-Oxoazetidin-2-yl)cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (7b): Compound **7b** was prepared by a similar procedure to that described for **7d**. $R_f=0.3$ (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=6.19$ (s, 1H), 5.77 (s, 1H), 4.22 (s, 1H), 3.79 (s, 6H), 3.20–3.08 (m, 5H), 2.78 ppm (dd, $J=14.75$, 2.04 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=167.8$, 167.5, 167.4, 133.2, 132.3, 131.1, 118.7, 52.8, 52.4, 43.6, 28.4, 26.3 ppm; IR (film): $\tilde{\nu}=3365$, 1722, 1265 cm^{-1}.

4-(4-Oxoazetidin-2-yl)cyclohex-4-ene-1,2-dicarboxylic acid dimethyl ester (7c): Compound **7c** was prepared by a similar procedure to that described for **7d**. M.p. 110 °C; $R_f=0.1$ (EtOAc/hexane 1:4); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=5.88$ (d, $J=10.04$, 1H), 5.74 (d, $J=9.60$, 1H), 4.09 (m, 1H), 3.71 (m, 6H), 3.20–3.18 (m, 1H), 2.93–2.87 (m, 2H), 2.78–2.74 (m, 1H), 2.44–2.29 (m, 2H), 2.24–2.17 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=174.82$, 174.79, 174.7, 174.6, 167.6, 167.5, 134.5, 134.4, 121.8, 121.1, 52.13, 52.09, 51.3, 51.2, 43.4, 43.5, 41.0, 40.9, 27.4, 27.1, 26.1, 25.8 ppm; IR (KBr): $\tilde{\nu}=3333$, 2953, 1735, 1196 cm^{-1}.

5-(4-Oxoazetidin-2-yl)-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7e): Compound **7e** was prepared by a similar procedure to that described for **7d**. $R_f=0.3$ (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta=7.48$–7.43 (m, 2H), 7.40–7.37 (m, 1H), 7.19 (d, $J=8.04$ Hz, 2H), 5.97 (dd, $J=6.54$, 3.26 Hz, 1H), 5.81 (d, $J=16.70$ Hz, 1H), 4.14 (s, 1H), 3.39–3.28 (m, 2H), 3.20–3.08 (m, 2H), 2.83–2.73 (m, 1H), 2.63–2.58 (m, 1H), 2.38–2.32 (m, 1H), 2.29–2.23 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): $\delta=178.7$, 178.6, 178.5, 167.1, 167.0, 139.2, 138.7, 129.2, 126.2, 123.7, 122.9, 50.8, 50.4, 44.1, 43.1, 39.6, 39.2, 24.5, 22.9 ppm; IR (film): $\tilde{\nu}=3309$, 2952, 1713, 1497, 734 cm^{-1}.

4-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}cyclohex-4-ene-1,1,2,2-tetracarbonitrile (7f): In a V-vial, a reaction mixture of **4** (140.7 mg, 0.5 mmol) and tetra(cyano)ethylene (128.1 mg, 1.0 mmol) in benzene (0.8 mL) was refluxed at 83 °C. After this mixture had been stirred for 5 h, it was poured into saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3×20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:1) to afford **7f** (175.6 mg, 86 %). M.p. 176 °C; R_f=0.6 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C, TMS): δ=8.23 (s, 1H), 5.83 (s, 1H), 4.08 (t, J=5.41 Hz, 1H), 4.00 (s, 1H), 3.51 (s, 1H), 3.45 (s, 1H), 3.34 (d, J=10.22 Hz, 1H), 3.14 (d, J=18.65 Hz, 1H), 2.83 (dd, J=2.31, 2.31 Hz, 1H), 1.10 (d, J=6.22 Hz, 3H), 0.79 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C, TMS): δ=167.1, 132.6, 116.3, 111.7, 111.6, 111.4, 64.9, 64.0, 51.7, 30.7, 30.2, 25.8, 22.2, 17.7, −4.2, −4.8 ppm; IR (KBr): $\tilde{\nu}$=3433, 1686, 707 cm^{-1}.

4-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (7g): In a V-vial, a reaction mixture of **4** (140.7 mg, 0.5 mmol) and dimethylacetylene dicarboxylate (98.1 mg, 1.0 mmol) in benzene (0.8 mL) was refluxed at 83 °C. After the mixture had been stirred for 48 h, it was poured into saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3×20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:3) to afford **7g** (175.7 mg, 83 %). M.p. 199 °C; R_f=0.1 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=6.00 (s, 1H), 5.76 (s, 1H), 4.20 (t, J=5.78 Hz, 1H), 4.13 (s, 1H), 3.79 (s, 6H), 3.09–3.05 (m, 3H), 2.99–2.94 (m, 1H), 2.89 (dd, J=2.13, 1.98 Hz, 1H), 1.24 (d, J=6.27 Hz, 3H), 0.88 (s, 9H), 0.09 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=168.3, 168.2, 167.9, 132.8, 132.5, 131.5, 118.0, 65.5, 64.7, 53.9, 52.3, 52.4, 28.3, 27.2, 25.7, 22.7, 17.9, −4.2, −4.7 ppm; IR (KBr): $\tilde{\nu}$=3310, 2953, 1729, 1263, 1263 cm^{-1}.

4-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}cyclohex-4-ene-1,2-dicarboxylic acid dimethyl ester (7h): Compound **7h** was prepared by a similar procedure to that described for **7g** by using **6c** (4 equiv). M.p. 92 °C; R_f=0.1 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=6.07 (s, 1H), 5.73 (d, J=5.16 Hz, 1H), 4.21–4.15 (m, 1H), 3.70 (s, 6H), 2.91–2.84 (m, 2H), 2.49 (t, J=16.46 Hz, 2H), 2.26–2.17 (m, 2H), 1.23 (dd, J=6.24, 6.09 Hz, 3H), 0.88 (s, 9H), 0.08 ppm (s, 6H); isomer B: δ=6.10 (s, 2H), 5.73 (d, J=5.16 Hz, 1H), 4.21–4.15 (m, 1H), 3.70 (s, 6H), 2.91–2.84 (m, 2H), 2.49 (t, J=16.46 Hz, 2H), 2.26–2.17 (m, 2H), 1.23 (dd, J=6.24, 6.09 Hz, 3H), 0.88 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=174.3, 174.1, 168.29, 134.1, 120.0, 65.3, 63.8, 53.8, 53.7, 51.4, 40.56, 40.48, 26.8, 25.1, 22.0, 17.3, 13.5, −5.3, −5.4 ppm; isomer B: δ=174.3, 174.2, 168.2, 134.2, 119.5, 64.9, 64.5, 53.8, 53.7, 51.4, 49.4, 40.41, 26.9, 25.1, 22.1, 20.4, 17.3, 13.5, −4.8, −5.3 ppm; IR (KBr): $\tilde{\nu}$=3324, 2953, 2249, 1653, 731 cm^{-1}.

4-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}cyclohex-4-ene-1,2-dicarboxylic acid dimethyl ester (7i): Compound **7i** was prepared by a similar procedure to that described for **7g** by using **6f** (4 equiv). R_f=0.1 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=5.96 (s, 1H), 5.71 (s, 1H), 4.22–4.19 (m, 1H), 4.11 (d, J=6.03 Hz, 1H), 3.69 (t, J=4.17 Hz, 6H), 3.08 (m, 2H), 2.87 (d, J=2.97, 1H), 2.58 (m, 2H), 2.34 (m, 2H), 1.25 (m, 3H), 0.88 (s, 9H), 0.08 ppm (s, 6H); isomer B δ=5.96 (s, 1H), 5.71 (s, 1H), 4.22–4.19 (m, 1H), 4.11 (d, J=6.03 Hz, 1H), 3.69 (t, J=4.17 Hz, 6H), 3.08 (m, 2H), 2.84 (d, J=2.61, 1H), 2.58 (m, 2H), 2.34 (m, 2H), 1.25 (m, 3H), 0.88 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=173.4, 173.1, 168.6, 134.8, 120.7, 65.5, 64.7, 54.3, 52.0, 39.9, 39.6, 25.7, 25.3, 22.6, 17.9, 14.2, −4.23, −4.84 ppm; isomer B: δ=173.2, 173.1, 168.6, 134.9, 120.9, 65.4, 64.6, 54.2, 51.9, 39.7, 34.6, 25.6, 25.4, 22.7, 17.9, 14.2, −4.27, −4.88 ppm; IR (film): $\tilde{\nu}$=3324, 2953, 2249, 1653, 731 cm^{-1}.

5-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7j): Compound **7j** was prepared by a similar procedure to that described for **7g**. M.p. 189 °C; R_f=0.2 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=7.85 (s, 1H), 5.95–5.91 (m, 1H), 5.80 (s, 1H), 4.25–4.17 (m, 2H), 3.21–3.15 (m, 2H), 2.70–2.65 (m, 2H), 1.14 (d, J=6.24 Hz, 3H), 0.87 (s, 9H), 0.08 ppm (s, 6H); isomer B δ=7.97 (s, 1H), 5.95–5.91 (m, 1H), 5.84 (s, 1H), 4.25–4.17 (m, 2H), 3.27–3.20 (m, 2H), 2.77–2.72 (m, 2H), 1.23 (d, J=6.21 Hz, 3H), 0.87 (s, 9H), 0.08 ppm (s, 6H); (100 MHz, $CDCl_3$, 25 °C, TMS): isomer A: δ=179.3, 179.0, 168.4, 138.9, 123.4, 65.0, 63.8, 53.4, 40.7, 40.3, 25.7, 24.0, 23.3, 22.7, 17.9, −4.2, −4.9 ppm; isomer B: δ=179.3, 179.0, 168.3, 139.2, 122.7, 65.0, 64.5, 52.9, 40.39, 40.32, 25.7, 24.0, 23.3, 22.6, 17.9, −4.2, −4.9 ppm; IR (KBr): $\tilde{\nu}$=3241, 2954, 1714, 1161, 778 cm^{-1}.

5-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}-2-propyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7k): In a V-vial, a reaction mixture of **4** (56.3 mg, 0.2 mmol), *N*-ethylmaleimide (50.0 mg, 0.4 mmol), and indium trichloride (1.9 mg, 0.01 mmol) in acetonitrile (0.3 mL) was stirred at 25 °C. After the reaction mixture had been stirred for 24 h, it was poured into saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3×20 mL), and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:3) to afford **7k** (75.6 mg, 93 %). M.p. 154 °C; R_f=0.4 (EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=5.88 (d, J=12.03 Hz, 2H), 4.24–4.15 (m, 1H), 4.11 (s, 1H), 3.49 (dd, J=7.16, 7.05 Hz, 2H), 3.16–3.07 (m, 3H), 2.24–2.08 (m, 2H), 1.25 (d, J=6.30, 3H), 1.09 (t, J=3.78, 7.16 Hz, 3H), 0.87 (s, 9H), 0.08 ppm (d, J=3.84 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=179.5, 179.3, 168.2, 139.1, 122.2, 65.0, 64.7, 52.8, 39.4, 39.0, 33.9, 25.7, 24.2, 23.1, 22.6, 17.9, 13.2, −4.2, −4.9 ppm; IR (KBr): $\tilde{\nu}$=3235, 2950, 1754, 778 cm^{-1}.

5-{3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-yl}-2-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (7l): Compound **7l** was prepared by a similar procedure to that described for **7k**. M.p. 193 °C; R_f=0.7 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.47 (t, J=7.62 Hz, 2H), 7.39 (t, J=7.12 Hz, 1H), 7.19 (d, J=7.73 Hz, 2H), 5.97 (t, J=3.24 Hz, 1H), 5.58 (s, 1H), 4.21 (t, J=8.06 Hz, 2H), 3.38–3.27 (m, 2H), 2.87–2.75 (m, 3H), 2.38–2.25 (m, 2H), 1.24 (d, J=3.12 Hz), 0.88 (s, 9H), 0.73 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=178.8, 178.6, 168.1, 139.4, 131.1, 129.2, 128.7, 126.2, 122.4, 65.0, 64.7, 52.8, 39.6, 39.1, 25.7, 24.5, 23.2, 22.6, 17.9, −4.2, −4.9 ppm; IR (KBr): $\tilde{\nu}$=3280, 2953, 1760, 1444, 777 cm^{-1}.

3-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-(9,10-dihydroxy-1,4-dihydroanthracen-2-yl)azetidin-2-one (7m): Compound **7m** was prepared by a similar procedure to that described for **7g**. M.p. 192 °C; R_f=0.6 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=8.12–8.09 (m, 2H), 7.74–7.71 (m, 2H), 5.93 (s, 1H), 5.86 (s, 1H), 4.27 (d, J=5.65 Hz, 2H), 3.32–3.29 (m, 2H), 3.26–3.23 (m, 2H), 2.97 (s, 1H), 1.28 (d, J=6.13 Hz, 3H), 0.91 (s, 9H), 0.12 ppm (d, J=4.67 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ=166.9, 133.1, 115.8, 110.3, 110.2, 110.1, 110.0, 66.2, 65.5, 53.0, 37.6, 37.4, 32.5, 32.4, 25.7, 17.9, −4.2, −4.6 ppm; IR (KBr): $\tilde{\nu}$=3184, 2926, 1755, 1669, 730 cm^{-1}.

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