HETEROCYCLES, Vol. 105, No. , 2022, pp. -. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 24th February, 2022, Accepted, 16th March, 2022, Published online, 24th March, 2022
DOI: 10.3987/COM-22-S(R)16

CONSTRUCTION OF TETRAHYDROQUINOLINES WITH SPIROCYCLIC STRUCTURES AT THE 4-POSITION

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This paper is dedicated to Professor Somsak Ruchirawat on the occasion of his 80th birthday.

Abstract – The construction of tetrahydroquinolines with a spirocyclic structure at the 4-position was studied. The five-step sequence includes construction of benzocyclopentanone oxime by Knoevenagel condensation of cyclic ketones with Meldrum's acid followed by Michael addition of aryl Grignard Reagent, intramolecular Friedel–Crafts acylation, condensation with hydroxylamine, and reductive ring expansion reaction using diisobutylaluminium hydride. The utility of this method was demonstrated by construction of a variety of tetrahydroquinolines possessing a four to eight-membered spirocyclic ring as well as adamantane and indane structures at the 4-position.

INTRODUCTION

Spirocyclic structures are often found in natural products, pharmaceuticals, functional materials, and chiral ligands used for asymmetric synthesis.[1] Such structures have attracted considerable attention in the design of drugs and functional materials, since incorporation of spirocyclic structures effectively improves the properties of organic molecules, such as solubility and metabolic stability.[2] Among the different spirocyclic compounds, we focused on tetrahydroquinoline derivatives having a spirocyclic ring at the 4-position. A number of polycyclic tetrahydroquinoline alkaloids possessing this structural motif have been isolated from nature, such as sesquiterpenoid, sespenine (**1**),[3] and aspernomine (**2**),[4] and marine alkaloid, discorhabdin C (**3**)[5] (Figure 1). In addition, tetrahydroquinolines bearing a spirocyclic ring at the 4-position such as **4**[6a] have been used as a basic structure for drug design.[6] For example, the tetrahydroquinolines **5** having a

spirocyclopentane ring at the 4-position displays inhibitory activity against 11β-hydroxydehydrogenase.[6b] Interestingly, the activity depends on the ring-size of the spirocyclic ring at the 4-position.[6] Despite recent recognition of the importance of tetrahydroquinolines having a spirocyclic structure in drug discovery, few general and versatile methodology for construction of these compounds has so far been reported. Therefore, we have initiated research aimed at establishing a general synthetic method for the tetrahydroquinoline skeleton with a spirocyclic structure at the 4-position.

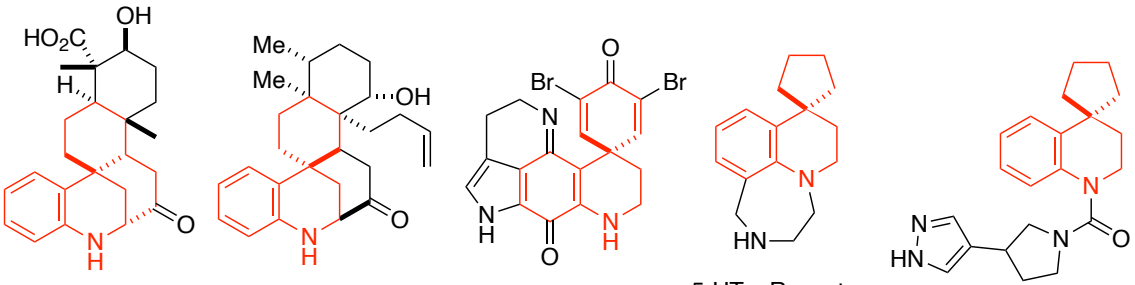
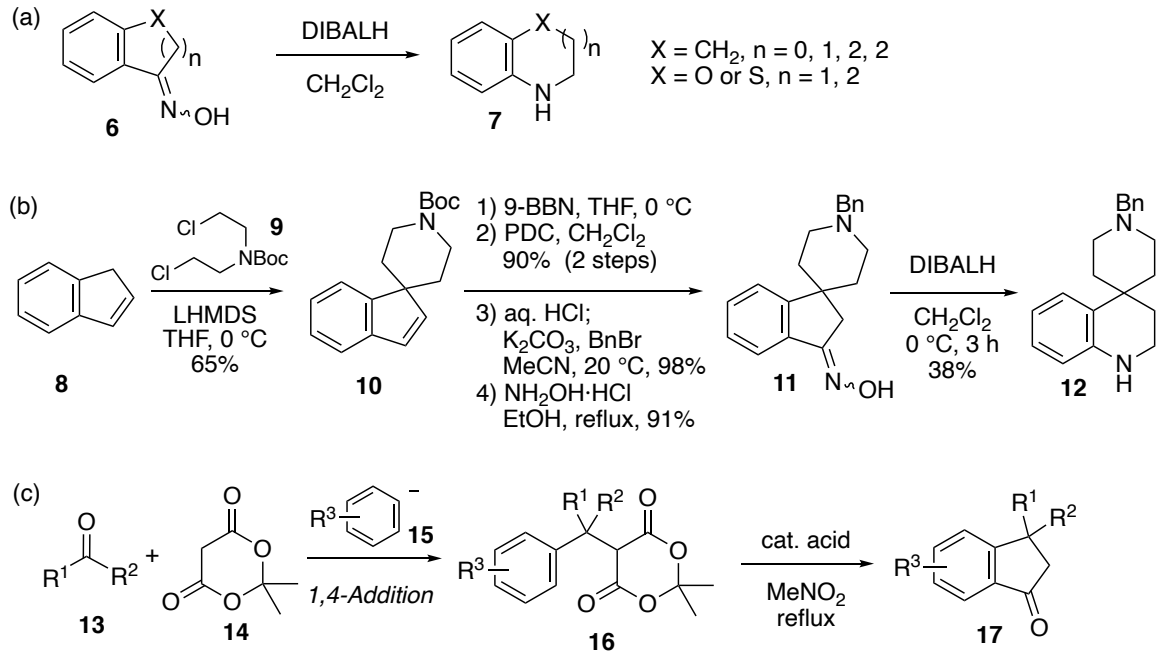


Figure 1. Drugs and Natural Product possessing a 4-Spirocyclic Tetrahydroquinoline Skeleton

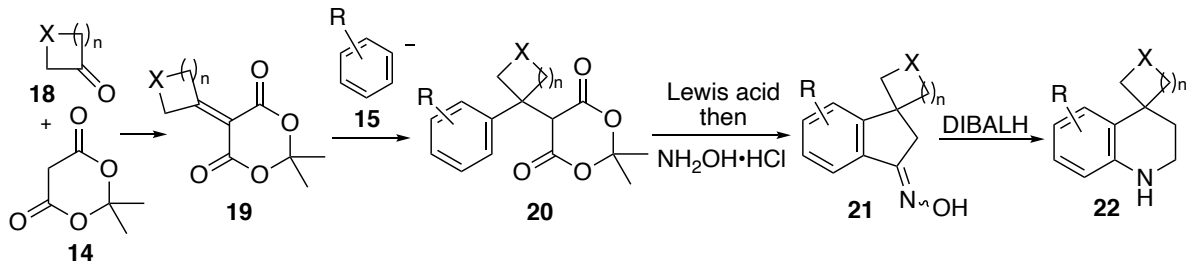
RESULTS AND DISCUSSIONS

Previously, our group conducted detailed studies on the reductive ring expansion reaction of cyclic ketoxime with diisobutylaluminium hydride (DIBALH) leading an *N*-containing heterocyclic ring.[7] Investigation on the scope of the substrate revealed that this protocol is applicable to construct a five to eight-membered *N*-containing heterocyclic ring fused with a benzene ring, including indoline, tetrahydroquinoline, tetrahydrobenzoazepine, and hexahydrobenzoazocine **7** (Scheme 1a). Goor and co-workers applied this reaction to indanone oxime **11** to construct a tetrahydroquinoline derivative bearing a spiropiperidine ring **12** (Scheme 1b).[8,9] However, Goor's synthesis required a lengthy sequence to prepare the indanone oxime from indene **8** and the spirocyclic structure in the products depended on a dihaloalkyl fragment such as **9**. As an alternative preparation of spirocyclic indanone derivatives, Chen reported a spirocyclization of indene and hydroboration/oxidative hydrolysis followed by oxidation with PDC.[10] Schwartzman utilized the Nazarov reaction with subsequent oxidative aromatization.[11] However, these protocols possess only a limited applicability. The most versatile strategy would be Fillion's protocol featuring intramolecular Friedel–Crafts acylation of ketene generated by thermolysis of Meldrum's acid derivative **16** (Scheme 1c).[12] They demonstrated its utility by constructing a broad range of indanone derivatives including those having a spirocyclic ring. Accordingly, we initiated research to develop a general scheme for construction of tetrahydroquinolines having a spiro structure by combining Fillion's intramolecular Friedel–Crafts acylation and our reductive ring expansion reaction of indanone oximes

(Scheme 2). In this paper, we describe a systematic investigation on the optimization and scope of this general scheme.

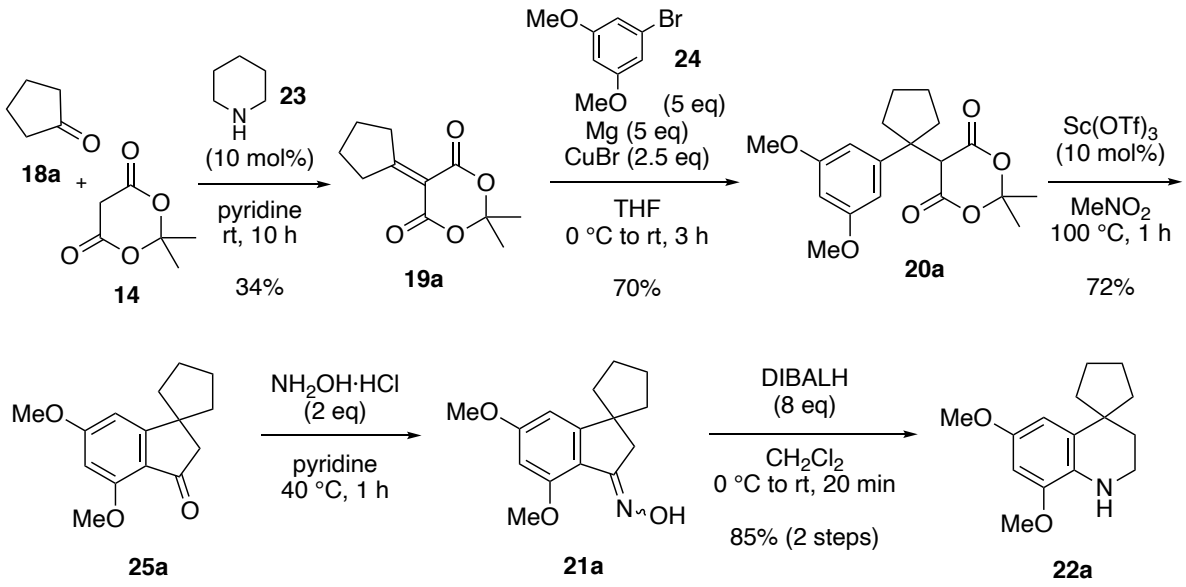


Scheme 1. Construction of Indanones and Tetrahydroquinolines by Reductive Ring Expansion of Indanone Oximes



Scheme 2. General Scheme for Construction of the Tetrahydroquinolines with a Spirocyclic Structure

First, we prepared an indanone oxime bearing a cyclopentane ring according to the Fillion's protocol, and conducted a reductive ring expansion reaction to examine the efficiency of the above general scheme (Scheme 2). Thus, Knoevenagel condensation using cyclopentanone (**18a**) and Meldrum's acid (**14**) in the presence of piperidine (**23**)[13] afforded cyclopentylidene Meldrum's acid **19a** in a modest yield. Then, Grignard reagent generated from 3,5-dimethoxybromobenzene was added to **19a** to produce **20a**. Upon treatment of **20a** with scandium trifluoromethanesulfonate ($Sc(OTf)_3$),[12] the expected Fillion's intramolecular Friedel–Crafts acylation proceeded via generation of the ketene intermediate by thermolysis of the Meldrum's acid moiety, and subsequent acylation afforded the desired indanone **25a** in 72% yield. Finally, conversion to the corresponding oxime **21a** and reductive ring expansion using excess DIBALH afforded tetrahydroquinoline with spiro cyclopentane at the 4-position **22a** in 85% yield over two steps.

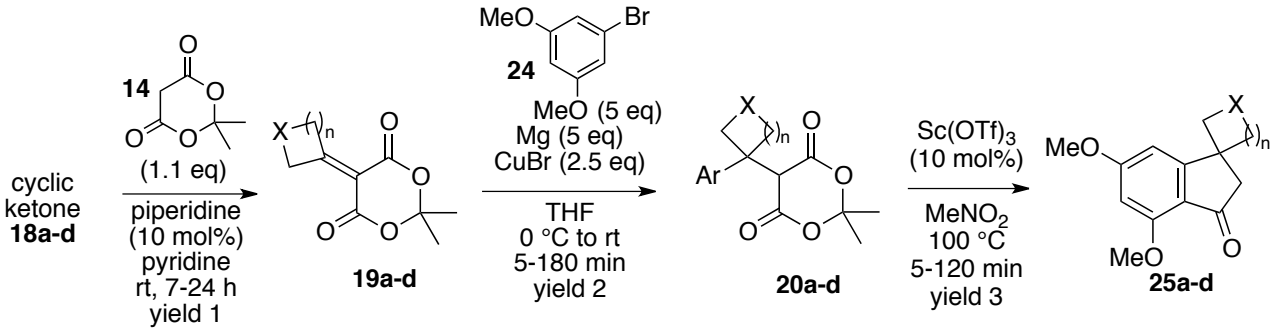


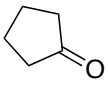
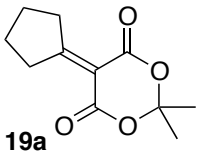
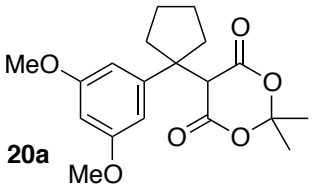
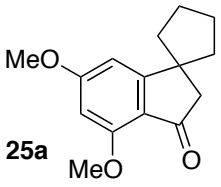
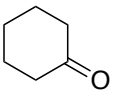
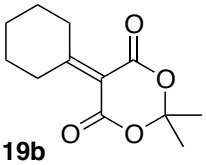
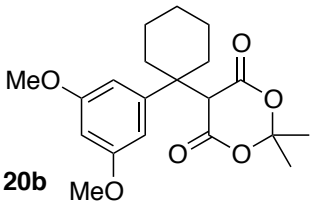
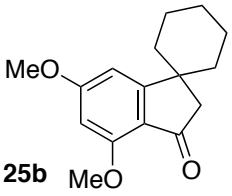
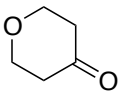
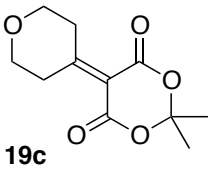
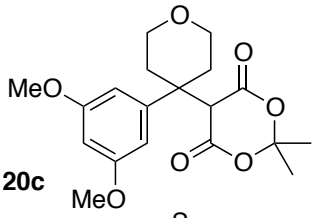
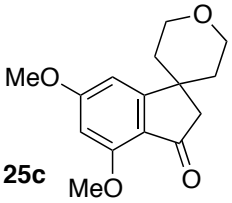
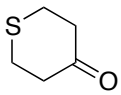
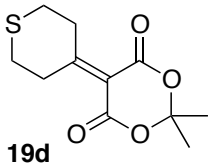
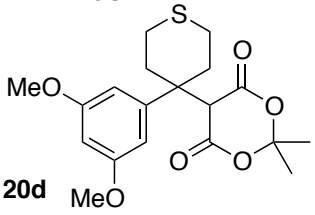
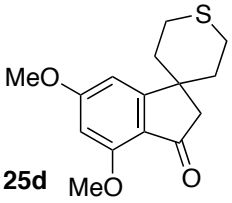
Scheme 3. Initial Investigation of the General Scheme using Cyclopentanone

Having confirmed the effectiveness of the general scheme, we then investigated its scope and feasibility for the construction of tetrahydroquinolines with a variety of spirocyclic rings. First, preparation of indanone derivatives using a series of six-membered cyclic ketones including cyclohexanone (**18b**), tetrahydro-4*H*-pyran-4-one (**18c**), and tetrahydro-4*H*-thiopyran-4-one (**18d**) (Table 1, entries 2-4) was examined. Knoevenagel condensation of **18b-d** with Meldrum's acid (**14**) and subsequent conjugated addition provided the desired **20b-d** in good to high yields. Then, intramolecular Friedel–Crafts acylation of **20b-d** proceeded as reported by Fillion and co-workers[12] to afford the corresponding spirocyclic indanones **25b-d** having cyclohexane, tetrahydropyran, and tetrahydrothiopyran rings, respectively, in good to high yields (Table 1, entries 2–4).[14]

We then applied both smaller and larger size cyclic ketones, including cyclobutanone (**18e**), cycloheptanone (**18f**), and cyclooctenone (**18g**), as the starting ketone. Unexpectedly, Knoevenagel condensation of cyclobutanone (**18e**) with Meldrum's acid (**14**) under the standard conditions using piperidine (**23**)[13] gave a mixture of the desired product and an inseparable side product. After extensive optimization, we found that a combination of acetic acid and ammonium acetate in toluene[15] provided the desired product **19e** in modest yield (Table 2, entry 1). The reaction of large-size cyclic ketones, such as cyclooctenone (**18f**) and cycloheptanone (**18g**), also proceeded using acetic acid and ammonium acetate to afford the desired products **19f** and **19g** in modest yields (entries 2 and 3). The following conjugated addition and intramolecular Friedel–Crafts acylation took place smoothly to produce the corresponding spirocyclic indanone derivatives **25e-g** having a 4, 7, or 8-membered ring at the benzylic position in high yields (entries 1–3).

Table 1. Construction of Indanones having 5 or 6-membered Spirocyclic Ring

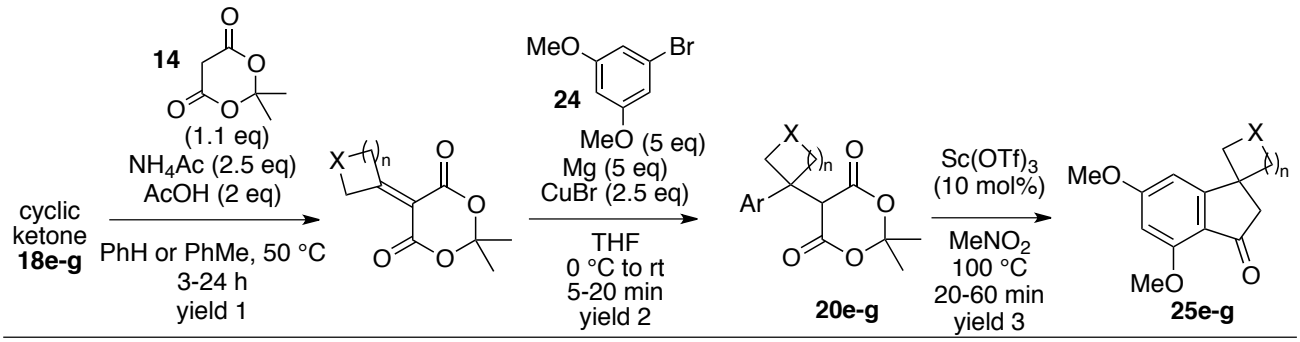


entry	ketone	product	yield 1 (%)	product	yield 2 (%)	product	yield 3 (%)
1			34		70		72
	18a	**19a**		**20a**		**25a**	
2			57		70		81
	18b	**19b**		**20b**		**25b**	
3			34		77		63
	18c	**19c**		**20c**		**25c**	
4			66[a]		76		84
	18d	**19d**		**20d**		**25d**	

[a]Product was isolated by recrystallization due to decomposition during column chromatography on silica gel.

Next, we conducted a three-step sequence using 2-adamantanone (**18h**) as a highly sterically demanding ketone (Table 3). While the initial Knoevenagel condensation with Meldrum's acid (**14**) provided the desired product in modest yield, 1,4-addition of aryl Grignard reagent to the sterically hindered adamantylidene Meldrum's acid **19h** under the standard conditions using copper(I) bromide (CuBr) did not proceed at all. Examination of a series of copper reagents revealed that copper(I) chloride (CuCl) was effective to promote the 1,4-addition to afford **20h** in 78% yield. The following intramolecular Friedel–Crafts acylation proceeded without an event to afford indanone derivative **25h** having a spiro adamantane structure in good yield.

Table 2. Construction of Indanones having a 4, 7, or 8-membered Spirocyclic Ring



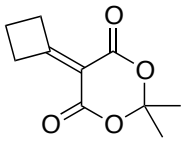
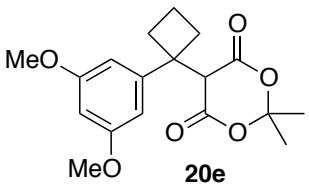
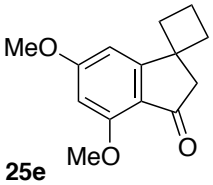
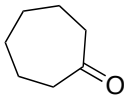
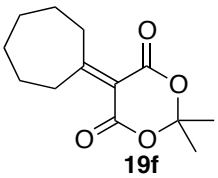
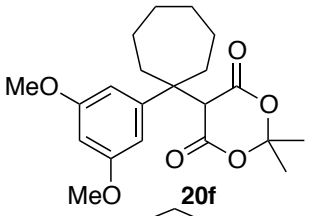
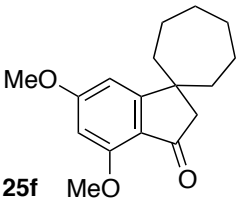
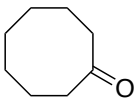
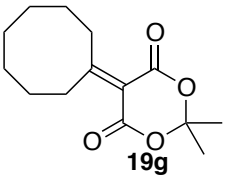
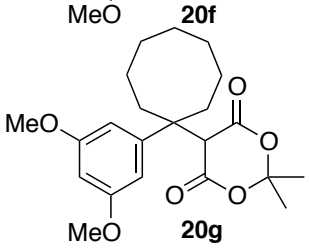
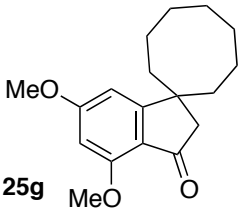
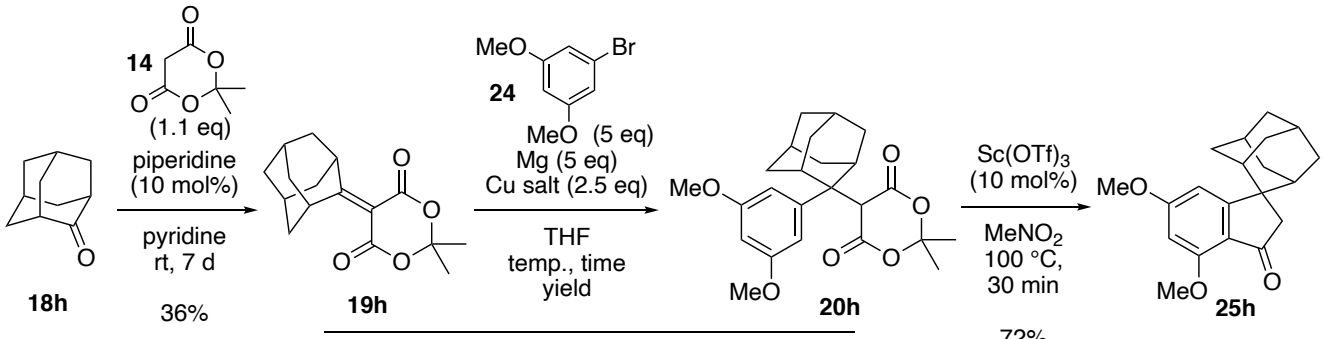
entry	ketone	product	yield 1 (%)	product	yield 2 (%)	product	yield 3 (%)
1	 **18e**	 **19e**	44	 **20e**	71	 **25e**	74
2	 **18f**	 **19f**	29	 **20f**	91	 **25f**	85
3	 **18g**	 **19g**	37	 **20g**	82	 **25g**	79

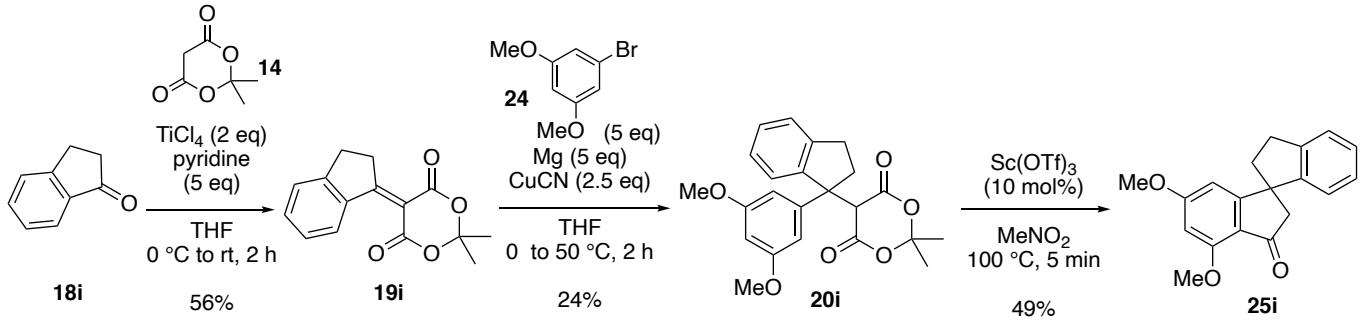
Table 3. Construction of Indanones having a Spiro Adamantane Structure



entry	Cu salt	temp.	time (h)	yield (%)
1	CuBr	0 °C to reflux	4	N.R.
2	CuCl	0 to 50 °C	1	78
3	CuI	0 °C to reflux	5	<8
4	CuCN	0 °C to reflux	5	N.D.

N.D. = not detected.

Finally, indanone **18i** was used as the staring ketone. Knoevenagel condensation with Meldrum's acid (**14**) was conducted under conditions referenced from the literature[16] to provide product **19i** in 56% yield (Scheme 4). Conjugated addition of Grignard reagent to sterically hindered substrate **19i** using CuBr did not afford **20i**. Rather, an undesired reduction product of the carbon–carbon double bond **19i'** was obtained, possibly via single electron transfer from the Grignard reagent. After screening of the copper reagents, we found that reaction with CuCN afforded the desired **20i** as the major product, although the yield was low.[17] Intramolecular Friedel–Crafts acylation took place smoothly to produce the corresponding indanone derivative having a spiro indane ring **25i**.



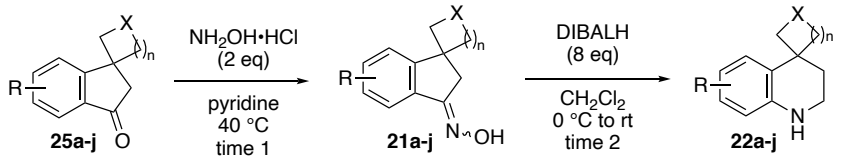
Scheme 4. Construction of Indanone having a Spiro Indane Structure

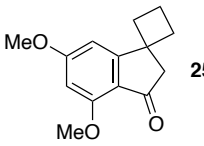
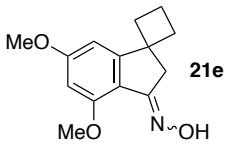
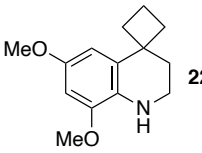
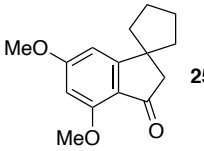
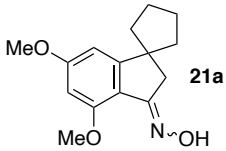
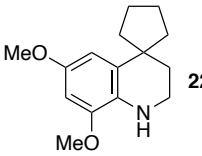
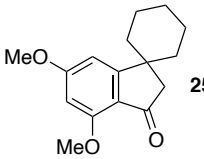
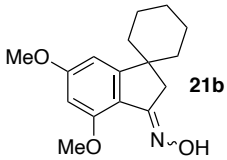
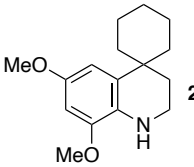
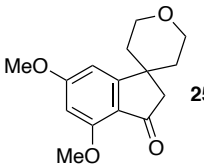
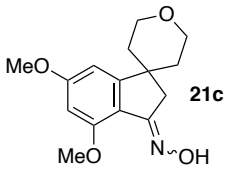
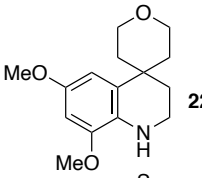
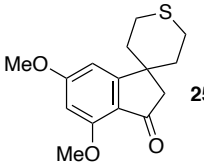
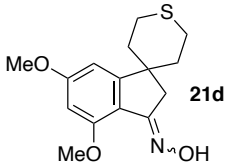
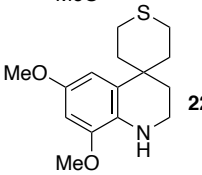
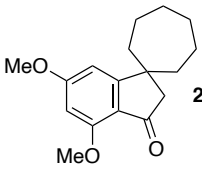
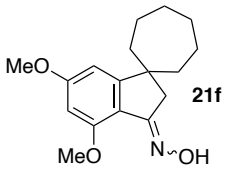
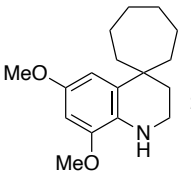
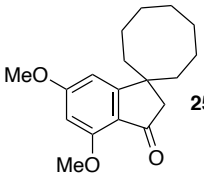
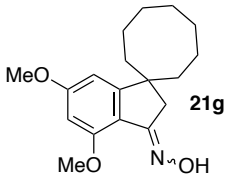
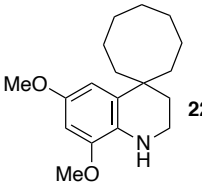
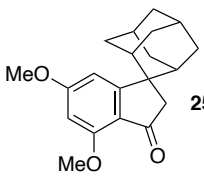
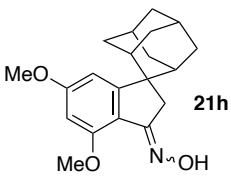
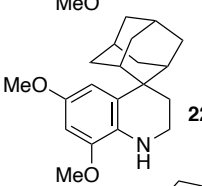
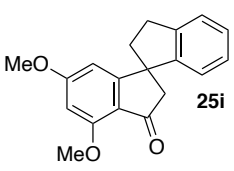
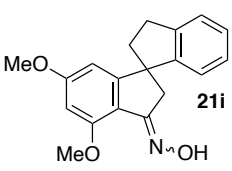
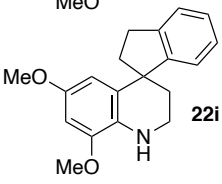
Having established the preparation of a variety of indanone derivative with a spirocyclic structure, we executed the key reductive ring expansion of indanone oxime formation to construct the corresponding tetrahydroquinolines having variety of spirocyclic rings (Table 4). Conversion of ketones **25a-i** to oximes **21a-i** smoothly proceeded under the standard conditions using two equivalents of hydroxylamine hydrochloride in pyridine at 40 °C. The oxime intermediates **21a-22i** thus obtained were subjected to the reductive ring expansion reaction with DIBALH. The expected two-step reaction took place uneventfully to produce the tetrahydroquinolines having a variety of spirocyclic rings **22a-i** including four to eight-membered carbocyclic rings, as well as tetrahydro-4*H*-pyran and tetrahydro-4*H*-thiopyran in high overall yields in two steps (entries 1–7). Furthermore, the key reaction proved to be feasible to construct structurally more complicated tetrahydroquinoline derivatives possessing spiro adamantane and indane in good to high yields (entries 8 and 9, respectively).

CONCLUSION

In summary, we have established a highly versatile protocol for construction of tetrahydroquinolines with a spirocyclic structure at the 4-position. Benzocyclopentanone oximes were readily assembled by a five-step sequence including Knoevenagel condensation of cyclic ketones with Meldrum's acid, Michael addition of Grignard Reagent, intramolecular Friedel–Crafts acylation, and condensation. The key

Table 4. Construction of Spirocyclic Tetrahydroquinolines by Oxime Formation and Reductive Ring Expansion Reaction with DIBALH



entry	ketone	time 1 (min)	oxime	time 2 (min)	product	yield over 2 steps (%)
1	 **25e**	30	 **21e**	15	 **22e**	59
2	 **25a**	60	 **21a**	20	 **22a**	85
3	 **25b**	180	 **21b**	60	 **22b**	81
4	 **25c**	60	 **21c**	25	 **22c**	76
5	 **25d**	60	 **21d**	20	 **22d**	78
6	 **25f**	60	 **21f**	5	 **22f**	62
7	 **25g**	50	 **21g**	20	 **22g**	82
8	 **25h**	50	 **21h**	20	 **22h**	85
9	 **25i**	120	 **21i**	20	 **22i**	67

reductive ring expansion reaction using DIBALH provided the desired tetrahydroquinolines. Utility of this method was demonstrated by construction of a variety of tetrahydroquinolines possessing four to eight-membered spirocyclic rings, as well as adamantane and indane structures.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. Anhydrous Et_2O, THF, and CH_2Cl_2 were purchased from Kanto Chemical Co. Inc. Anhydrous pyridine, toluene, benzene, and $MeNO_2$ were dried and distilled according to the standard protocols. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50 μm). Preparative TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. Analytical TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. NMR spectra were recorded on a JNM-AL400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, brs = broad singlet. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line at 77.0 ppm. IR spectra were measured on a SHIMADZU FTIR–8300 spectrometer. Mass spectra were recorded on a Brucker micrOTOF II (ESI).

General Procedure for Condensation of Ketones with Meldrum's Acid

5-Cyclopentylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (19a)

A 30-mL round-bottomed flask equipped with a magnetic stirring bar was charged with cyclopentanone (**18a**) (840 μL, 9.46 mmol), Meldrum's acid (**14**) (1.50 g, 10.4 mmol), and anhydrous pyridine (9.46 mL). To the stirred resulting mixture was added piperidine (**23**) (87 μL, 0.95 mmol) at room temperature. The resulting mixture was stirred at room temperature for 10 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of cyclopentanone (**18a**). The solvents of the resulting mixture were azeotropically removed with toluene under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/EtOAc = 3:1) to afford cyclopentylidene Meldrum's acid **19a** (679 mg, 3.23 mmol, 34%) as a white solid. R_f = 0.34 (hexanes/EtOAc = 3:1); Mp 78–80 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3018, 2969, 2876, 1718, 1597, 1392, 1299, 1274, 1216, 1012, 920, 747; ^{1}H NMR (400 MHz, $CDCl_3$): d 3.22–3.12 (m, 4H), 1.89–1.79 (m, 4H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): d 194.4, 161.2, 110.8, 103.6, 38.8, 27.4, 25.5; HRMS (ESI$^-$) calcd. for $C_{11}H_{13}O_4$ (M–H$^+$), 209.0819; found, 209.0819.

General Procedure for Michael Addition

5-(1-(3,5-Dimethoxyphenyl)cyclopentyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20a)

A flame-dried 20-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with Mg turnings (85.7 mg, 3.57 mmol). The flask was evacuated under heating for 20 min, then backfilled with argon. After addition of dry THF (3.57 mL), 3,5-dimethoxybromobenzene (**24**) (775 mg, 3.57 mmol) was added portionwise to the flask at room temperature. The reaction mixture was stirred for 2 h at room temperature until all magnesium was dissolved. Another flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with CuBr (256 mg, 1.79 mmol) and dry THF (1.79 mL). The resulting mixture was cooled to 0 °C. To the resulting mixture was transferred the Grignard reagent-THF solution *via* cannula. The mixture was stirred for 10 min at 0 °C. Another flame-dried 10-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with cyclopentylidene Meldrum's acid **19a** (150 mg, 0.714 mmol) and dry THF (2.38 mL). To the Cuprate reagent-THF solution was transferred the resulting mixture *via* cannula. The mixture was stirred for 3 h at room temperature, after which time TLC (hexane/EtOAc = 3:1) indicated complete consumption of cyclopentylidene Meldrum's acid **19a**. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexane/acetone = 5:1) to afford Michael adduct **20a** (174 mg, 0.500 mmol, 70%) as a white solid. R_f = 0.37 (hexanes/ethyl acetate = 3:1); Mp 115–117 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3020, 2959, 2877, 2836, 1735, 1595, 1458, 1425, 1283, 1205, 1157, 1064, 992, 849, 750; ^1H NMR (400 MHz, $CDCl_3$): d 6.48 (d, *J* = 2.0 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 1H), 3.76 (s, 6H), 3.41 (s, 1H), 2.46–2.28 (m, 4H), 1.90–1.70 (m, 2H), 1.66–1.53 (m, 5H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d 165.0, 160.8, 143.4, 106.0, 105.4, 99.4, 55.9, 55.3, 54.7, 38.0, 29.9, 27.1, 21.7; HRMS (ESI^+) calcd. for $C_{19}H_{24}NaO_6$ ($M+Na^+$), 371.1465; found, 371.1447.

General Procedure for Friedel–Crafts Acylation

4',6'-Dimethoxyspiro[cyclopentane-1,1'-inden]-3'(2'*H*)-one (25a)

A flame-dried 20-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, a reflux condenser, and a three-way stopcock was charged with Michael adduct **20a** (200 mg, 0.574 mmol) and anhydrous $MeNO_2$ (5.74 mL). To the stirred resulting mixture was added $Sc(OTf)_3$ (28.3 mg, 57.4 μmol) at 100 °C. The resulting mixture was heated for 20 min, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of Michael adduct **20a**. The resulting mixture was filtered through

a pad of Celite and the filter cake was washed thoroughly with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/EtOAc = 1:1) to afford indanone **25a** (102 mg, 0.412 mmol, 72%) as a white solid. R_f = 0.27 (hexanes/EtOAc = 1:1); Mp 101–102 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3011, 2949, 2869, 1685, 1585, 1460, 1329, 1312, 1235, 1211, 1156, 1107, 1059, 1027, 849, 748; ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.52 (s, 2H), 2.00–1.70 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 167.3, 167.1, 159.3, 119.0, 99.0, 97.1, 55.8, 55.7, 53.1, 49.4, 41.8, 24.9; HRMS (ESI^+) calcd. for $C_{15}H_{19}O_3$ ($M+H^+$), 247.1329; found, 247.1325.

5-Cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (19b)

According to the general procedure described for cyclopentylidene Meldrum's acid **19a**, cyclohexylidene Meldrum's acid **19b** was prepared from cyclohexanone (**18b**) in 18.9 mmol scale (2.40 g, 10.7 mmol, 57%); a white solid; R_f = 0.33 (hexanes/EtOAc = 3:1); Mp 85–87 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3024, 2994, 2940, 2861, 1727, 1445, 1293, 1198, 1109, 1016, 934, 775, 748; ^1H NMR (400 MHz, $CDCl_3$): δ 2.95 (t, *J* = 6.0 Hz, 4H), 1.85 (quin, *J* = 6.0 Hz, 4H), 1.79–1.67 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1, 161.0, 114.0, 103.6, 34.5, 29.5, 26.9, 25.8; HRMS (ESI^-) calcd. for $C_{12}H_{15}O_4$ ($M–H^+$), 223.0976; found, 223.0967.

5-(1-(3,5-Dimethoxyphenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20b)

According to the general procedure described for Michael adduct **20a**, Michael adduct **20b** was prepared from cyclohexylidene Meldrum's acid **19b** in 1.34 mmol scale (341 mg, 0.940 mmol, 70%); a white solid; R_f = 0.33 (hexanes/EtOAc = 3:1); Mp 135–137 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3016, 2936, 2867, 1742, 1596, 1457, 1424, 1294, 1206, 1159, 1061, 761; ^1H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, *J* = 2.0 Hz, 2H), 6.36 (t, *J* = 2.0 Hz, 1H), 3.76 (s, 6H), 3.44 (s, 1H), 2.52–2.35 (m, 2H), 2.13–1.92 (m, 2H), 1.74–1.59 (m, 2H), 1.53–1.37 (m, 7H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 161.1, 142.2, 106.1, 105.6, 99.3, 56.6, 55.4, 47.4, 35.8, 30.5, 26.6, 25.6, 22.5; HRMS (ESI^+) calcd. for $C_{20}H_{26}NaO_6$ ($M+Na^+$), 385.1622; found, 385.1606.

4',6'-Dimethoxyspiro[cyclohexane-1,1'-inden]-3'(2'*H*)-one (25b)

According to the general procedure described for indanone **25a**, indanone **25b** was prepared from Michael adduct **20b** in 0.414 mmol scale (87.1 mg, 0.335 mmol, 81%); a white solid; R_f = 0.27 (hexanes/EtOAc = 1:1); Mp 132–134 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3006, 2928, 2854, 1685, 1583, 1456, 1317, 1201, 1154, 1058, 1031, 749; ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (d, *J* = 2.4 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.55 (s, 2H), 1.85–1.23 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

201.9, 169.3, 166.9, 159.1, 117.7, 99.4, 97.3, 55.8, 55.7, 49.2, 42.8, 38.3, 25.5, 23.7; HRMS (ESI^+) calcd. for $C_{16}H_{21}O_3$ ($M+H^+$), 261.1485; found, 261.1482.

2,2-Dimethyl-5-(tetrahydro-4*H*-pyran-4-ylidene)-1,3-dioxane-4,6-dione (19c)

According to the general procedure described for cyclopentylidene Meldrum's acid **19a**, tetrahydropyran-4-ylidene Meldrum's acid **19c** was prepared from tetrahydropylan-4-one (**18c**) in 3.78 mmol scale (294 mg, 1.30 mmol, 34%); a white solid; R_f = 0.64 (hexanes/acetone = 1:1); Mp 190 °C (decomposition); IR (ATR, cm^{-1}): 2999, 2953, 2842, 1725, 1497, 1278, 1216, 1146, 1105, 1042, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 3.89 (t, *J* = 5.6 Hz, 2H), 3.16 (t, *J* = 5.6 Hz, 2H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): d 175.7, 160.7, 115.1, 104.0, 68.9, 35.0, 27.1; HRMS (ESI^-) calcd. for $C_{11}H_{15}O_5$ ($M–H^+$), 225.0768; found, 225.0777.

5-(4-(3,5-Dimethoxyphenyl)tetrahydro-2*H*-pyran-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20c)

According to the general procedure described for Michael adduct **20a**, Michael adduct **20c** was prepared from tetrahydropyran-4-ylidene Meldrum's acid **19c** in 1.16 mmol scale (327 mg, 0.898 mmol, 77%); a pale yellow solid; R_f = 0.20 (hexanes/EtOAc = 1:1); Mp 155–157 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3020, 2959, 2858, 1766, 1738, 1597, 1459, 1420, 1288, 1219, 1159, 776; ^1H NMR (400 MHz, $CDCl_3$): δ 6.46 (s, 3H), 3.87 (ddd, *J* = 12.0, 4.0, 4.0 Hz, 2H), 3.77 (s, 6H), 3.62–3.49 (m, 3H), 2.53 (ddd, *J* = 13.6, 4.0, 4.0 Hz, 2H), 2.32 (ddd, *J* = 13.6, 9.6, 4.0 Hz, 2H), 1.54 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 161.4, 140.9, 105.9, 105.8, 99.5, 64.1, 55.7, 55.4, 45.4, 36.1, 30.3, 26.7; HRMS (ESI^+) calcd. for $C_{19}H_{24}NaO_7$ ($M+Na^+$), 387.1414; found, 387.1405.

4,6-Dimethoxy-2',3',5',6'-tetrahydrospiro[indene-1,4'-pyran]-3(2*H*)-one (25c)

According to the general procedure described for indanone **25a**, indanone **25c** was prepared from Michael adduct **20c** in 0.548 mmol scale (91.1 mg, 0.347 mmol, 63%); a white solid; R_f = 0.16 (hexanes/EtOAc = 1:1); Mp 212–214 °C (hexanes/EtOAc, white solid); IR (ATR, cm^{-1}): 3017, 2848, 1693, 1602, 1585, 1321, 1219, 1162, 1109, 1058, 1031, 753; ^1H NMR (400 MHz, $CDCl_3$): δ 6.53 (d, *J* = 1.6 Hz, 1H), 6.34 (d, *J* = 1.6 Hz, 1H), 4.03 (dd, *J* = 12.0, 4.4 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.55 (ddd, *J* = 12.0, 12.0, 1.2 Hz, 2H), 2.65 (s, 2H), 2.12 (ddd, *J* = 12.0, 12.0, 4.4 Hz, 2H), 1.47–1.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 167.3, 167.2, 159.5, 118.0, 99.4, 97.7, 65.5, 55.9, 55.8, 48.6, 40.3, 38.2; HRMS (ESI^+) calcd. for $C_{15}H_{19}O_4$ ($M+H^+$), 263.1278; found, 263.1282.

2,2-Dimethyl-5-(tetrahydro-4*H*-thiopyran-4-ylidene)-1,3-dioxane-4,6-dione (19d)

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrothiopyran-4-one (**18d**) (1.10 g, 9.46 mmol), Meldrum's acid (**14**) (1.50 g, 10.4 mmol), and

anhydrous pyridine (9.46 mL). To the stirred resulting mixture was added piperidine (**23**) (86.8 μL, 0.946 mmol) at room temperature. The resulting mixture was stirred at room temperature for 14 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of tetrahydrothiopyran-4-one (**18d**). The solvents of the resulting mixture were azeotropically removed with toluene under reduced pressure to give a crude material, which was recrystallized with MeOH to afford tetrahydrothiopyran-4-ylidene Meldrum's acid **19d** (1.52 g, 6.26 mmol, 66%) as a yellow solid. R_f = 0.33 (hexanes/EtOAc = 1:1); Mp 145–147 °C (hexanes/EtOAc, yellow needle); IR (ATR, cm^{-1}): 1758, 1726, 1601, 1292, 1219, 1196, 771; ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (t, *J* = 6.0 Hz, 4H), 3.02 (t, *J* = 6.0 Hz, 4H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 160.6, 115.2, 104.0, 36.8, 32.8, 27.1; HRMS (ESI^-) calcd. for $C_{11}H_{13}O_4S$ ($M–H^+$), 241.0528; found, 241.0540.

5-(4-(3,5-Dimethoxyphenyl)tetrahydro-2*H*-thiopyran-4-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20d)

According to the general procedure described for Michael adduct **20a**, Michael adduct **20d** was prepared from tetrahydrothiopyran-4-ylidene Meldrum's acid **19d** in 0.619 mmol scale (180 mg, 0.473 mmol, 76%); a pale yellow solid; R_f = 0.19 (hexanes/EtOAc = 3:1); Mp 138-140 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3025, 2963, 2836, 1736, 1596, 1455, 1423, 1291, 1216, 1203, 1158, 747; ^1H NMR (400 MHz, $CDCl_3$): δ 6.39 (s, 3H), 3.77 (s, 6H), 3.45 (s, 1H), 2.90–2.62 (m, 6H), 2.40 (ddd, *J* = 13.6, 10.4, 3.2 Hz, 2H), 1.53 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 161.3, 140.5, 106.0, 105.8, 99.3, 56.5, 55.4, 46.4, 36.6, 30.4, 26.6, 24.2; HRMS (ESI^+) calcd. for $C_{19}H_{24}NaO_6S$ ($M+H^+$), 403.1186; found, 403.1179.

4,6-Dimethoxy-2',3',5',6'-tetrahydrospiro[indene-1,4'-thiopyran]-3(2*H*)-one (25d)

According to the general procedure described for indanone **25a**, indanone **25d** was prepared from Michael adduct **20d** in 0.368 mmol scale (86.1 mg, 0.309 mmol, 84%); a white solid; R_f = 0.19 (hexanes/EtOAc = 1:1); Mp 206–207 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 1774, 1741, 1688, 1587, 1408, 1348, 1317, 1218, 1158, 1056, 771, 742; ^1H NMR (400 MHz, $CDCl_3$): δ 6.53 (d, *J* = 2.0 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.83 (ddd, *J* = 14.0, 14.0, 2.4 Hz, 2H), 2.66–2.55 (m, 2H), 2.53 (s, 2H), 2.10 (ddd, *J* = 14.0, 14.0, 3.2 Hz, 2H), 1.86–1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 167.9, 167.2, 159.2, 117.4, 99.4, 97.8, 55.9, 55.8, 48.0, 41.8, 38.5, 25.7; HRMS (ESI^+) calcd. for $C_{15}H_{19}O_3S$ ($M+H^+$), 279.1049; found, 279.1052.

5-Cyclobutylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (19e)

A centrifuge tube equipped with a magnetic stirring bar was charged with cyclobutanone (**18e**) (0.300 mL, 4.01 mmol), Meldrum's acid (**14**) (578 mg, 4.01 mmol), NH_4OAc (618 mg, 8.02 mmol), AcOH (459 mL,

9.86 mmol), and anhydrous toluene (5.73 mL). The resulting mixture was heated to 50 °C for 3 h, after which time TLC (hexanes/EtOAc = 3:1) indicated complete consumption of cyclobutanone (**18d**). To the resulting mixture was added H_2O, and the mixture was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/EtOAc = 3:1) to afford cyclobutylidene Meldrum's acid **19e** (342 mg, 1.74 mmol, 44%) as a yellow solid. R_f = 0.31 (hexanes/EtOAc = 3:1); Mp 98–100 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 2923, 2854, 1725, 1589, 1454, 1421, 1287, 1261, 1153, 1064, 830, 779; ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (t, *J* = 8.0 Hz, 4H), 2.33 (quin, *J* = 8.0 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 160.2, 110.6, 104.4, 36.9, 27.6, 18.5; HRMS (ESI^-) calcd. for $C_{10}H_{12}O_4$ ($M–H^+$), 195.0663; found, 195.0654.

5-(1-(3,5-Dimethoxyphenyl)cyclobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20e)

According to the general procedure described for Michael adduct **20a** (using CuCl instead of CuBr), Michael adduct **20e** was prepared from cyclobutylidene Meldrum's acid **19e** in 2.04 mmol scale (483 mg, 1.45 mmol, 71%); a white solid; R_f = 0.25 (hexanes/EtOAc = 3:1); Mp 103–105 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3001, 2949, 2839, 1740, 1596, 1455, 1425, 1291, 1204, 1156, 1039, 757; ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (d, *J* = 2.4 Hz, 2H), 6.34 (t, *J* = 2.4 Hz, 1H), 3.82 (s, 1H), 3.76 (s, 6H), 3.01–2.88 (m, 2H), 2.72–2.59 (m, 2H), 2.09–1.96 (m, 1H), 1.95–1.79 (m, 1H), 1.58 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 160.7, 145.3, 105.9, 105.2, 99.6, 55.4, 55.2, 50.5, 34.9, 29.2, 27.6, 16.8; HRMS (ESI^+) calcd. for $C_{18}H_{22}NaO_6$ ($M+Na^+$), 357.1309; found, 357.1294.

4',6'-Dimethoxyspiro[cyclobutane-1,1'-inden]-3'(2'*H*)-one (25e)

According to the general procedure described for indanone **25a**, indanone **25e** was prepared from Michael adduct **20e** in 0.598 mmol scale (103 mg, 0.445 mmol, 74%); a white solid; R_f = 0.24 (hexanes/EtOAc = 1:1); Mp 54–56 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3030, 2991, 2919, 2860, 1724, 1693, 1600, 1463, 1330, 1285, 1157, 1059, 768, 742; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.87 (s, 2H), 2.53–2.40 (m, 2H), 2.30–1.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 167.3, 166.7, 158.7, 118.5, 99.2, 97.2, 55.8, 55.7, 53.1, 44.1, 35.9, 16.3; HRMS (ESI^+) calcd. for $C_{14}H_{17}O_3$ ($M+H^+$), 233.1172; found, 233.1175.

5-Cycloheptylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (19f)

A 200-mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with cycloheptanone (**18f**) (3.59 mL, 30.4 mmol), Meldrum's acid (**14**) (5.00 g, 34.7 mmol), NH_4OAc (539

mg, 6.99 mmol), AcOH (2.18 mL, 38.0 mmol), and anhydrous benzene (30.4 mL). The resulting mixture was heated to 50 °C for a day. To the resulting mixture was added H_2O, and the mixture was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/acetone = 6:1) to afford cycloheptylidene Meldrum's acid **19f** (2.09 g, 8.76 mmol, 29%) as a pale yellow solid. R_f = 0.48 (hexanes/acetone = 5:1); Mp 48–49 °C (hexanes/EtOAc, white solid); IR (ATR, cm^{-1}): 3003, 2925, 2863, 1733, 1267, 1231, 1203, 1148, 741; ^1H NMR (400 MHz, $CDCl_3$): δ 3.04 (t, J = 6.0 Hz, 4H), 1.90–1.78 (m, 4H), 1.72 (s, 6H), 1.63–1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.3, 161.0, 115.7, 103.3, 36.7, 31.5, 28.1, 27.0, 26.1, 22.6, 14.0; HRMS (ESI^-) calcd. for $C_{13}H_{17}O_4$ ($M–H^+$), 237.1132; found, 237.1136.

5-(1-(3,5-Dimethoxyphenyl)cycloheptyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20f)

According to the general procedure described for Michael adduct **20a** (using CuCl instead of CuBr), Michael adduct **20f** was prepared from cycloheptylidene Meldrum's acid **19f** in 3.78 mmol scale (1.30 g, 3.43 mmol, 91%); a white solid; R_f = 0.37 (hexanes/EtOAc = 3:1); Mp 85–87 °C (hexanes/EtOAc, colorless prisms); IR (ATR, cm^{-1}): 3209, 2957, 2874, 2836, 1747, 1685, 1585, 1423, 1282, 1199, 1071, 1004, 775, 737; ^1H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, J = 2.4 Hz, 2H), 6.36 (t, J = 2.4 Hz, 1H), 3.77 (s, 6H), 3.40 (s, 1H), 2.38–2.28 (m, 4H), 1.72–1.36 (m, 11H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 160.7, 144.8, 106.3, 105.5, 98.7, 57.8, 55.3, 50.7, 36.6, 30.3, 29.4, 26.6, 22.5; HRMS (ESI^+) calcd. for $C_{21}H_{28}NaO_6$ ($M+Na^+$), 399.1778; found, 399.1765.

4',6'-Dimethoxyspiro[cycloheptane-1,1'-inden]-3'(2'*H*)-one (25f)

According to the general procedure described for indanone **25a**, indanone **25f** was prepared from Michael adduct **20f** in 2.39 mmol scale (559 mg, 2.04 mmol, 85%); a white solid; R_f = 0.25 (hexanes/EtOAc = 1:1); Mp 95–97 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3004, 2919, 2849, 1717, 1697, 1600, 1462, 1324, 1276, 1208, 1158, 744; ^1H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, J = 2.0 Hz, 1H), 6.29 (d, J = 2.0 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.58 (s, 2H), 1.95–1.45 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 170.5, 167.0, 158.9, 117.3, 99.4, 97.0, 55.8, 55.7, 50.6, 45.5, 41.7, 28.3, 24.5; HRMS (ESI^+) calcd. for $C_{17}H_{23}O_3$ ($M+H^+$), 275.1642; found, 275.1653.

5-Cyclooctylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (19g)

A 30-mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with cyclooctanone (**18g**) (0.802 mL, 6.10 mmol), Meldrum's acid (**14**) (1.00 g, 6.94 mmol), NH_4OAc (135 mg, 1.75 mmol), AcOH (0.437 mL, 7.63 mmol), and anhydrous benzene (6.10 mL). The resulting mixture

was heated to 50 °C for a day. To the resulting mixture was added H_2O, and the mixture was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/acetone = 9:1) to afford cyclooctylidene Meldrum's acid **19g** (574 mg, 2.28 mmol, 37%) as a white solid. R_f = 0.39 (hexanes/acetone = 5:1); Mp 82–84 °C (hexanes/EtOAc, colorless plate); IR (ATR, cm^{-1}): 1717, 1573, 1186, 984, 923, 804, 752; ^1H NMR (400 MHz, $CDCl_3$): δ 3.05 (t, *J* = 6.0 Hz, 4H), 2.00–1.88 (m, 4H), 1.71 (s, 6H), 1.59–1.49 (m, 4H), 1.43–1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): d 189.9, 161.1, 114.8, 103.1, 35.5, 27.2, 27.1, 26.0; HRMS (ESI^-) calcd. for $C_{14}H_{19}O_4$ ($M–H^+$), 251.1289; found, 251.1286.

5-(1-(3,5-Dimethoxyphenyl)cyclooctyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20g)

According to the general procedure described for Michael adduct **20a** (using CuCl instead of CuBr), Michael adduct **20g** was prepared from cyclooctylidene Meldrum's acid **19g** in 0.317 mmol scale (103 mg, 0.263 mmol, 82%); a colorless amorphous; R_f = 0.38 (hexanes/EtOAc = 3:1); IR (ATR, cm^{-1}): 2994, 2924, 2852, 1744, 1597, 1456, 1423, 1283, 1205, 1158, 1065, 856, 752; ^1H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, *J* = 2.0 Hz, 2H), 6.36 (t, *J* = 2.0 Hz, 1H), 3.76 (s, 6H), 3.43 (s, 1H), 2.43–2.17 (m, 4H), 1.74–1.43 (m, 13H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 160.7, 143.6, 106.4, 105.6, 99.1, 55.9, 55.3, 51.1, 31.3, 30.6, 28.3, 26.5, 25.5, 22.9; HRMS (EI) calcd. for $C_{22}H_{30}O_6$ (M^+), 390.2042; found, 390.2039.

4',6'-Dimethoxyspiro[cyclooctane-1,1'-inden]-3'(2'*H*)-one (25g)

According to the general procedure described for indanone **25a**, indanone **25g** was prepared from Michael adduct **20g** in 0.197 mmol scale (44.8 mg, 0.155 mmol, 79%); a white amorphous; R_f = 0.32 (hexanes/ EtOAc = 1:1); Mp 150–152 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 2934, 2857, 2834, 1740, 1593, 1454, 1422, 1267, 1200, 1152, 1066, 781; ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (d, *J* = 2.0 Hz, 1H), 6.30 (d, *J* = 2.0 Hz, 1H), 3.91(s, 3H), 3.90 (s, 3H), 2.53 (s, 2H), 1.93–1.47 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 169.2, 166.5, 159.0, 117.5, 100.5, 96.8, 55.8, 55.7, 52.6, 45.4, 36.9, 28.3, 24.3, 23.7; HRMS (ESI^+) calcd. for $C_{18}H_{25}O_3$ ($M+H^+$), 289.1798; found, 289.1791.

5-((1*r*,3*r*,5*r*,7*r*)-Adamantan-2-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (19h)

A 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 2-adamantanone (**18h**) (500 mg, 3.33 mmol), Meldrum's acid (**14**) (576 mg, 3.99 mmol), and anhydrous pyridine (4.00 mL). To the stirred resulting mixture was added piperidine (**23**) (30 μL, 0.33 mmol) at room temperature. The resulting mixture was stirred at room temperature for 7 days, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of 2-adamantanone (**18h**). To the resulting mixture was added H_2O, and

the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/EtOAc = 3:1) to afford adamantylidene Meldrum's acid **19h** (333 mg, 1.21 mmol, 36%) as a white solid. Mp 210–211 °C (hexanes/EtOAc, white powder); R_f = 0.40 (hexanes/EtOAc = 1:1); IR (ATR, cm^{-1}): 3205, 2924, 2856, 1723, 1588, 1271, 1217, 1200, 771, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 4.10–4.02 (m, 2H), 2.17–2.07 (m, 4H), 2.07–1.90 (m, 8H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 161.1, 111.8, 103.5, 40.3, 36.11, 36.09, 27.0, 26.8; HRMS (ESI^+) calcd. for $C_{16}H_{20}O_4K$ ($M+K^+$), 315.0999; found, 315.0996.

5-((1*R*,3*S*,5*r*,7*r*)-2-(3,5-Dimethoxyphenyl)adamantan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20h)

According to the general procedure described for Michael adduct **20a** (using CuCl instead of CuBr), Michael adduct **20h** was prepared from adamantylidene Meldrum's acid **19h** in 0.651 mmol scale (212 mg, 0.511 mmol, 78%); a white solid; R_f = 0.24 (toluene/EtOAc = 10:1); Mp 166–168 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3012, 2914, 1726, 1596, 1457, 1423, 1293, 1217, 771, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 6.42 (d, *J* = 2.0 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 1H), 4.26 (s, 1H), 3.75 (s, 6H), 3.00–2.93 (m, 2H), 2.42–2.30 (m, 2H), 2.07–1.99 (m, 1H), 1.99–1.81 (m, 4H), 1.78–1.61 (m, 5H), 1.49 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 161.2, 143.1, 105.6, 105.1, 99.2, 55.4, 53.0, 51.0, 38.4, 33.8, 33.4, 31.8, 30.5, 26.9, 26.8, 26.5; HRMS (ESI^+) calcd. for $C_{24}H_{30}NaO_6$ ($M+Na^+$), 437.1935; found, 437.1934.

(1*R*,3*S*,5*r*,7*r*)-4',6'-Dimethoxyspiro[adamantane-2,1'-inden]-3'(2'*H*)-one (25h)

According to the general procedure described for indanone **25a**, indanone **25h** was prepared from Michael adduct **20h** in 0.362 mmol scale (81.8 mg, 0.262 mmol, 72%); a white solid. R_f = 0.32 (hexanes/EtOAc = 1:1); Mp 155–157 °C (hexanes/EtOAc, white needle); IR (ATR, cm^{-1}): 3009, 2909, 1686, 1589, 1458, 1219, 1201, 1158, 772, 746; ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 1.2 Hz, 1H), 6.38 (d, *J* = 1.2 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.80 (s, 2H), 2.64–2.54 (m, 2H), 2.12–2.00 (m, 3H), 1.96–1.89 (m, 1H), 1.86–1.81 (m, 2H), 1.80–1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 165.6, 165.5, 159.3, 118.8, 107.0, 96.1, 55.8, 55.6, 52.5, 48.4, 39.7, 37.1, 36.2, 33.0, 27.2, 26.7; HRMS (ESI^+) calcd. for $C_{20}H_{25}O_3$ ($M+H^+$), 313.1798; found, 313.1790.

5-(2,3-Dihydro-1*H*-inden-1-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (19i)

A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with dry CH_2Cl_2 (10.5 mL). To the solvents was added $TiCl_4$

(4.57 mL, 41.6 mmol) dropwise at 0 °C. Another flame-dried 500-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with dry THF (78.6 mL). The resulting mixture was cooled to 0 °C. To the resulting mixture was transferred the $TiCl_4$-CH_2Cl_2 solution *via* cannula. Another flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with 1-indanone (**18i**) (2.75 g, 20.8 mmol), Meldrum's acid (**14**) (3.00 g, 20.8 mmol), and dry THF (10.5 mL). The resulting mixture was cooled to 0 °C. To the $TiCl_4$-THF solution was transferred the resulting mixture *via* cannula. Another flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with pyridine (8.38 mL, 104 mmol) and dry THF (10.5 mL). To the resulting mixture was transferred the pyridine-THF solution *via* cannula. The resulting mixture was warmed to room temperature and stirred for 2 h, after which time TLC (hexanes/acetone = 5:1) indicated complete consumption of 1-indanone (**18i**). The reaction mixture was quenched with H_2O, and the mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexane/acetone = 5:1) to afford indenylidene Meldrum's acid **19i** (3.02 g, 11.7 mmol, 56%) as a yellow solid. R_f = 0.28 (hexanes/acetone = 5:1); Mp 155–157 °C (hexanes/EtOAc, yellow plate); IR (ATR, cm^{-1}): 3022, 1715, 1549, 1292, 1266, 1198, 1058, 919, 869, 745, 665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 8.0 Hz, 1H), 7.56 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.60 (t, *J* = 5.2 Hz, 2H), 3.15 (t, *J* = 5.2 Hz, 2H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 162.6, 161.4, 155.7, 137.1, 134.4, 129.8, 127.1, 125.6, 109.6, 103.5, 36.9, 30.5, 27.1; HRMS (ESI^-) calcd. for $C_{15}H_{15}O_4$ ($M+H^+$), 257.0819; found, 257.0820.

5-(1-(3,5-Dimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20i) and 5-(2,3-dihydro-1*H*-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (19i')

According to the general procedure described for Michael adduct **20a** (using CuCN instead of CuBr), Michael adduct **20i** (a pale yellow solid; 18.4 mg, 0.0464 mmol, 24%) and reductant **19i'** (a white solid; 5.9 mg, 0.023 mmol, 12%) was obtained from indenylidene Meldrum's acid **19i** in 0.194 mmol scale.

5-(1-(3,5-Dimethoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (20i)

R_f = 0.28 (hexanes/acetone = 5:1); Mp 108–110 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3017, 2945, 1747, 1598, 1289, 1206, 1155, 770, 751, 665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.30–7.16 (m, 3H), 6.38 (d, *J* = 2.0 Hz, 2H), 6.29 (t, *J* = 2.0 Hz, 1H), 4.52 (s, 1H), 3.73 (s, 6H), 3.10–2.76 (m, 3H), 2.67 (ddd, *J* = 8.8, 4.4, 4.4 Hz, 1H), 1.82 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d 163.3, 162.9, 160.6, 148.0, 144.8, 144.1, 127.7, 126.4, 125.1, 125.0, 105.0, 104.7, 97.0, 57.3, 55.2, 55.1,

39.4, 30.6, 28.4, 27.1; HRMS (EI) calcd. for $C_{23}H_{24}O_6$ (M^+), 396.1573; found, 396.1608.

5-(2,3-Dihydro-1*H*-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (19i')

R_f = 0.08 (hexanes/acetone = 5:1); Mp 109–111 °C (hexanes/EtOAc, white powder); IR (ATR, cm^{-1}): 3001, 2929, 2849, 1785, 1748, 1594, 1454, 1380, 1297, 1204, 1056, 988, 896, 755; ^{1}H NMR (400 MHz, $CDCl_3$): d 7.24 (d, *J* = 7.6 Hz, 1H), 7.22–7.10 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 4.30 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1H), 3.96 (d, *J* = 2.8 Hz, 1H), 3.14 (ddd, *J* = 14.8, 8.8, 4.4 Hz, 1H), 2.92 (ddd, *J* = 14.8, 8.8, 8.8 Hz, 1H), 2.45 (dddd, *J* = 13.2, 8.8, 8.8, 4.4 Hz, 1H), 2.20–2.06 (m, 1H), 1.80 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 164.4, 144.5, 142.1, 127.2, 126.3, 124.9, 122.5, 104.9, 49.7, 43.6, 31.5, 29.0, 28.3, 27.3; HRMS (ESI^+) calcd. for $C_{15}H_{16}O_4$ (M^+), 260.1049; found, 260.1067.

4,6-Dimethoxy-2',3'-dihydro-1,1'-spirobi[inden]-3(2*H*)-one (25i)

According to the general procedure described for indanone **25a**, indanone **25i** (a yellow amorphous; 182 mg, 0.617 mmol, 49%) was obtained from Michael adduct **20i** in 1.25 mmol scale; R_f = 0.21 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3004, 2939, 2844, 1669, 1600, 1457, 1326, 1238, 1205, 1157, 1052, 834, 761; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.0 Hz, 1H), 7.28–7.19 (m, 1H), 7.15 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 2.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 3.95 (s, 3H), 3.77 (s, 3H), 3.14–3.06 (m, 2H), 2.93 (d, *J* = 18.0 Hz, 1H), 2.79 (d, *J* = 18.0 Hz, 1H), 2.47 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 2.33 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 167.3, 166.5, 158.9, 148.7, 143.2, 127.12, 127.10, 124.4, 122.8, 118.7, 100.0, 97.7, 55.8, 55.7, 54.1, 53.0, 42.8, 31.1; HRMS (ESI^+) calcd. for $C_{19}H_{19}O_3$ ($M+H^+$), 295.1329; found, 295.1332.

General Procedure for Oximation and Reductive Ring Expansion

6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclopentane-1,4'-quinoline] (22a)

A 20-mL round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser was charged with indanone **25a** (68.8 mg, 0.279 mmol), hydroxylamine hydrochloride (39.0 mg, 0.559 mmol) and anhydrous pyridine (2.79 mL). The resulting mixture was heated to 40 °C for 1 h, after which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of indanone **25a**. To the resulting mixture was added H_2O, and the mixture was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude oxime **21a** as a white solid. A crude oxime **21a** was used for the next reaction without further purification.

A 20-mL round-bottomed flask equipped with a magnetic stirring bar was charged with crude oxime **21a** and dry CH_2Cl_2 (2.79 mL). To the mixture was added DIBALH (1.00 M in hexane, 2.23 mL, 2.23 mmol) dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 20 minutes, after

which time TLC (hexanes/EtOAc = 1:1) indicated complete consumption of oxime **21a**. The reaction mixture was quenched with saturated aqueous Rochelle salt, and the mixture was stirred for 12 h at room temperature. The mixture was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel column chromatography (hexanes/EtOAc = 7:1) to afford tetrahydroquinoline **22a** (57.8 mg, 0.234 mmol, 85% from **21a** over 2 steps) as a yellow oil. R_f = 0.67 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3408, 2927, 2851, 1595, 1499, 1464, 1270, 1197, 1149, 1119, 1056, 1041, 937, 825; ^1H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 4.04 (brs, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.25 (t, *J* = 5.6 Hz, 2H), 2.00–1.60 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 147.0, 130.7, 128.5, 102.8, 96.2, 55.8, 55.4, 43.9, 42.9, 39.3, 36.0, 25.3; HRMS (ESI^+) calcd. for $C_{15}H_{22}NO_2$ ($M+H^+$), 248.1645; found, 248.1654.

6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclobutane-1,4'-quinoline] (22e)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22e** was prepared from indanone **25e** in 0.225 mmol scale (30.8 mg, 0.132 mmol, 59%); a colorless oil; R_f = 0.42 (hexanes/EtOAc = 2:1); IR (neat, cm^{-1}): 3411, 2933, 2834, 1596, 1500, 1297, 1209, 1193, 1150, 1132, 938, 825; ^1H NMR (400 MHz, $CDCl_3$): δ 6.68 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 3.98 (brs, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.22 (t, *J* = 5.6 Hz, 2H), 2.49–2.37 (m, 2H), 2.13–1.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 147.1, 129.6, 127.8, 102.7, 96.6, 55.9, 55.4, 39.5, 38.5, 36.1, 35.4, 14.8; HRMS (ESI^+) calcd. for $C_{14}H_{20}NO_2$ ($M+H^+$), 234.1489; found, 234.1492.

6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclohexane-1,4'-quinoline] (22b)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22b** was prepared from indanone **25b** in 0.222 mmol scale (46.3 mg, 0.177 mmol, 81%); a yellow oil; R_f = 0.68 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3406, 2927, 2851, 1594, 1499, 1464, 1374, 1245, 1197, 1149, 1056, 1040, 937, 825; ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (d, *J* = 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 4.05 (brs, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.21 (t, *J* = 6.0 Hz, 2H), 1.94 (t, *J* = 6.0 Hz, 2H), 1.80–1.47 (m, 8H), 1.40–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 147.1, 131.9, 128.5, 102.7, 96.3, 55.8, 55.4, 38.3, 37.8, 35.3, 30.3, 26.0, 21.6; HRMS (ESI^+) calcd. for $C_{16}H_{24}NO_2$ ($M+H^+$), 262.1802; found, 262.1799.

6',8'-Dimethoxy-2,2',3,3',5,6-hexahydro-1'*H*-spiro[pyran-4,4'-quinoline] (22c)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22c** was prepared from indanone **25c** in 0.251 mmol scale (49.9 mg, 0.189 mmol, 76%); a pale pink solid; R_f = 0.62 (ethyl acetate); Mp 106–108 °C (hexanes/EtOAc, pale pink solid); IR (ATR, cm^{-1}): 2955, 1690, 1599, 1586,

1500, 1269, 1219, 1198, 1147, 1040, 777; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 4.11 (brs, 1H), 3.90–3.79 (m, 5H), 3.79–3.66 (m, 5H), 3.23 (t, *J* = 6.0 Hz, 2H), 2.19 (ddd, *J* = 14, 14, 3.6 Hz, 2H), 2.07 (t, *J* = 6.0 Hz, 2H), 1.62–1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 147.2, 130.0, 128.8, 102.4, 97.0, 63.7, 55.9, 55.5, 38.5, 37.8, 33.2, 30.4; HRMS (ESI^+) calcd. for $C_{15}H_{22}NO_3$ ($M+H^+$), 264.1594; found, 264.1604.

6,8-Dimethoxy-2,2',3,3',5',6'-hexahydro-1*H*-spiro[quinoline-4,4'-thiopyran] (22d)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22d** was prepared from indanone **25d** in 0.180 mmol scale (39.4 mg, 0.141 mmol, 78%); a white solid; R_f = 0.75 (hexanes/EtOAc = 1:1); Mp 82–84 °C (hexanes/EtOAc, pale yellow needle); IR (ATR, cm^{-1}): 3390, 2935, 2836, 1597, 1498, 1373, 1272, 1210, 1153, 1055, 1036, 940, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 4.09 (brs, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.22 (t, *J* = 6.0 Hz, 2H), 3.02 (ddd, *J* = 14.0, 14.0, 1.6 Hz, 2H), 2.52–2.38 (m, 2H), 2.16 (ddd, *J* = 14.0, 14.0, 4.0 Hz, 2H), 2.03–1.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 147.2, 130.4, 128.3, 102.1, 96.9, 55.8, 55.5, 38.6, 37.3, 34.1, 29.6, 23.4; HRMS (ESI^+) calcd. for $C_{15}H_{22}NO_2S$ ($M+H^+$), 280.1366; found, 280.1360.

6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[cycloheptane-1,4'-quinoline] (22f)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22f** was prepared from indanone **25f** in 1.09 mmol scale (186 mg, 0.675 mmol, 62%); a yellow oil; R_f = 0.59 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3418, 2923, 2850, 1593, 1501, 1460, 1414, 1291, 1270, 1200, 1147, 1098, 1056, 1035, 940, 824; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (d, *J* = 2.4 Hz, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 4.03 (brs, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.27 (t, *J* = 6.0 Hz, 2H), 2.04–1.90 (m, 2H), 1.83 (t, *J* = 6.0 Hz, 2H), 1.76–1.47 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 146.7, 132.7, 127.2, 102.7, 95.9, 55.7, 55.3, 41.6, 37.8, 37.7, 34.2, 30.1, 23.4; HRMS (ESI^+) calcd. for $C_{17}H_{26}NO_2$ ($M+H^+$), 276.1958; found, 276.1969.

6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[cyclooctane-1,4'-quinoline] (22g)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22g** was prepared from indanone **25g** in 0.104 mmol scale (24.6 mg, 0.0850 mmol, 82%); a brown oil; R_f = 0.70 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3423, 2919, 2849, 1592, 1503, 1472, 1362, 1271, 1195, 1154, 1057, 938; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.52 (d, *J* = 2.4 Hz, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 4.07 (brs, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.32 (t, *J* = 2.0 Hz, 2H), 2.14–1.96 (m, 2H), 1.77 (t, *J* = 2.0 Hz, 2H), 1.75–1.45 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 146.7, 131.1, 127.1, 103.3, 96.1, 55.9, 55.4, 37.6, 37.3, 36.1, 34.5, 28.9, 25.5, 23.1; HRMS (ESI^+) calcd. for $C_{18}H_{28}NO_2$ ($M+H^+$), 290.2115; found, 290.2111.

(1*R*,3*S*,5*r*,7*r*)-6',8'-Dimethoxy-2',3'-dihydro-1'*H*-spiro[adamantane-2,4'-quinoline] (22h)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22h** was prepared from indanone **25h** in 0.160 mmol scale (42.8 mg, 0.137 mmol, 85%); a red amorphous; R_f = 0.83 (hexanes/EtOAc = 1:1); IR (neat, cm^{-1}): 3418, 2908, 1588, 1500, 1473, 1196, 1152, 1128, 1058, 1042, 934, 827, 755; ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, *J* = 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.01 (brs, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.38 (t, *J* = 7.2 Hz, 2H), 2.29–2.13 (m, 6H), 1.95–1.80 (m, 4H), 1.78–1.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 146.6, 132.1, 128.3, 104.6, 95.8, 56.0, 55.5, 42.1, 39.3, 37.7, 35.0, 33.9, 31.9, 30.8, 28.0, 27.8; HRMS (ESI^+) calcd. for $C_{20}H_{28}NO_2$ ($M+H^+$), 314.2115; found, 314.2106.

6',8'-Dimethoxy-2,2',3,3'-tetrahydro-1'*H*-spiro[indene-1,4'-quinoline] (22i)

According to the general procedure described for tetrahydroquinoline **22a**, tetrahydroquinoline **22i** was prepared from indanone **25i** in 0.499 mmol scale (99.1 mg, 0.335 mmol, 67%); a yellow oil; R_f = 0.28 (hexanes/EtOAc = 7:1); IR (neat, cm^{-1}): 3410, 2938, 1599, 1502, 1455, 1272, 1198, 1148, 1120, 1054, 1019, 940, 830, 763, 743; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.22 (m, 1H), 7.22–7.10 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.89 (d, *J* = 2.4 Hz, 1H), 4.13 (brs, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 3.44–3.31 (m, 2H), 3.05–2.96 (m, 2H), 2.33 (ddd, *J* = 12.6, 12.6, 7.2 Hz, 1H), 2.22 (ddd, *J* = 12.6, 7.2, 4.0 Hz, 1H), 2.03 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 2.03 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 1.93 (ddd, *J* = 12.6, 4.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 151.2, 147.1, 143.5, 128.9, 128.6, 126.64, 126.56, 124.3, 124.2, 104.3, 96.9, 55.7, 55.4, 50.3, 43.6, 39.2, 35.0, 29.9; HRMS (ESI^+) calcd. for $C_{19}H_{22}NO_2$ ($M+H^+$), 296.1645; found, 296.1645.

ACKNOWLEDGEMENTS

This work was financially supported by KAKENHI (JP26253001, JP18H02549, JP21H02601) from JSPS and Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP20am0101100.

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