

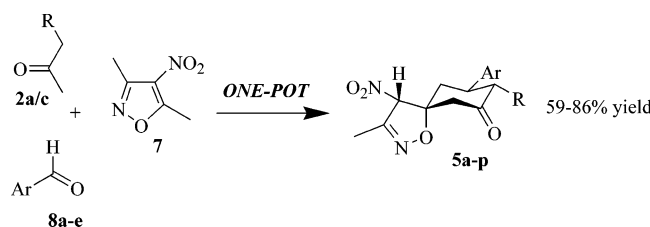
Multicomponent Synthesis of Spiroisoxazolines

Mauro F. A. Adamo,^{*,†} Donato Donati,[‡] Eleanor F. Duffy,[†] and Piero Sarti-Fantoni[§]

Centre for Synthesis and Chemical Biology (CSCB), Department of Pharmaceutical and Medicinal Chemistry, The Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2, Dublin, Ireland, Dipartimento di Chimica, Università di Siena, Via Aldo Moro, Siena 53100, Italy, and Dipartimento di Chimica Organica "U. Schiff", Università di Firenze, Via della Lastruccia, Sesto Fiorentino 50019, Italy

madamo@rcsi.ie

Received June 11, 2005



A three-component one-pot procedure (3-MCR) was developed to assemble the spiroisoxazoline nucleus from commercially available materials. This new methodology affords the title compounds in high yields and without the use of chromatography.

Introduction

The discovery of new agents displaying high antimicrobial activity is an important topic of research in medicinal chemistry.¹ Spiroisoxazolines are heterocyclic nuclei which have stimulated much interest in medicinal and biological chemistry.²⁻⁷ Following the first reports of their herbicidal and plant hormonal activity,² some naturally occurring spiroisoxazolines have been found useful in other biomedical areas (Figure 1). Examples include the naturally occurring araplysillins, which have been found to inhibit ATP-ase enzymes,³ and naturally occurring agelorin, a spiroisoxazoline derived from bromotyrosine which has proved active against pathogens

such as *Bacillus subtilis* and *Micrococcus luteus*.⁴ Also zamamistatin, a natural product isolated from the Okinawan sponge *Pseudoceratina purpurea*, exhibits a significant antibacterial activity against *Rhodospirillum salixigens*.⁵ Aerothionin displays antimycobacterial activity.⁶ More recently it was found that spiroisoxazoline containing SJ755 shows a remarkable integrin antagonist behavior, showing a new application for spiroisoxazoline-containing compounds.⁷

Results and Discussion

As a part of our endeavors to develop diversity-oriented syntheses using polyfunctional scaffolds such as 3-methyl-4-nitro-5-styrylisoxazole (**1**), we discovered a new reaction in which **1** reacted with acetylacetone (**2a**), ethyl acetoacetate (**2b**), and acetone (**2c**) (Scheme 1).⁸ The reaction was completed by an acidic workup to furnish spiroisoxazolines **5a-c** in good isolated yields. In this reaction, two Michael additions occurred consecutively that formed the 4-nitrospiroisoxazoline core as nitronate ammonium salts **4a-c**, which gave the final product **5a-c** after treatment with aqueous acid (Scheme 1). We also established that compounds **3a-c** or **5a-c** could be selectively obtained depending on the amount of base employed.

Spiroisoxazolines **5a-c** precipitated out as a single diastereoisomer.⁸ Remarkably in this reaction a total of

* To whom correspondence should be addressed. Phone: +353-1-4022208. Fax: +353-1-4022168.

[†] The Royal College of Surgeons in Ireland.

[‡] Università di Siena.

[§] Università di Firenze.

(1) Overbye, K. M.; Barrett, J. F. *Drug Discovery Today* **2005**, *10*, 45. Rogers, B. L. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 211.

(2) Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603. De Amici, M.; De Micheli, M.; Misani, V. *Tetrahedron* **1990**, *46*, 1975. Smetana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 1291.

(3) Faulkner, J. *Nat. Prod. Rep.* **2001**, *18*, 1.

(4) Wright, A. D.; King, G. M.; Sticher, O. *J. Nat. Prod.* **1990**, *53*, 1615.

(5) Takada, N.; Watanabe, R.; Suenaga, K.; Yamada, K.; Ueda, K.; Kita, M.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 5265.

(6) Encarnación-Dimayuga, R.; Ramírez, M. R.; Luna-Herrera, J. *Pharm. Biol.* **2003**, *41*, 384.

(7) Cue, D.; Southern, S. O.; Southern, P. J.; Prabhakar, J.; Lorelli, W.; Smallheer, J. M.; Mousa, S. A.; Cleary, P. P. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2858.

(8) Adamo, M. F. A.; Chimichi, S.; De Sio F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron Lett.* **2002**, *43*, 4157. Adamo, M. F. A.; Chimichi, S.; Donati, D.; Sarti-Fantoni, P. *Acta Crystallogr.* **2002**, *E58*, o-1125-o1127.

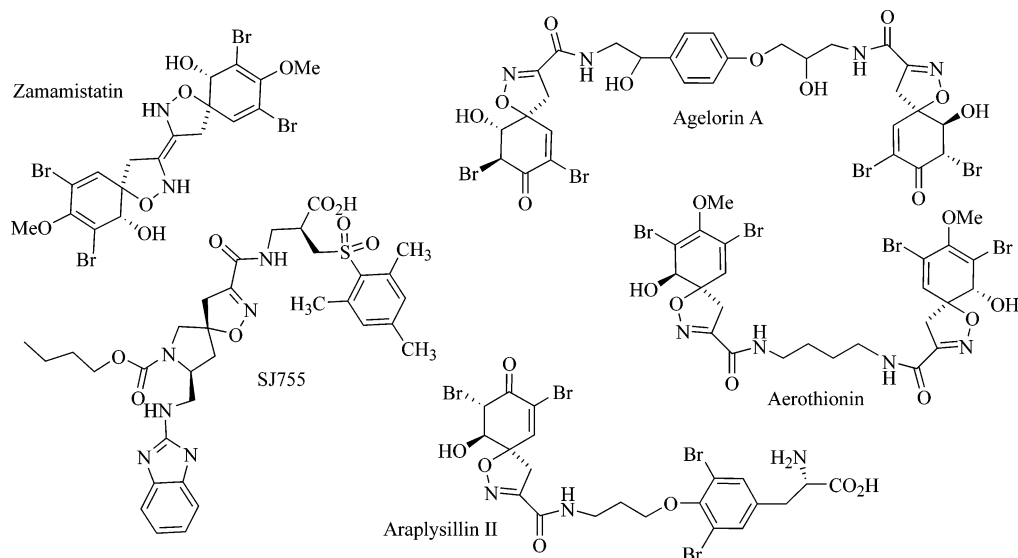
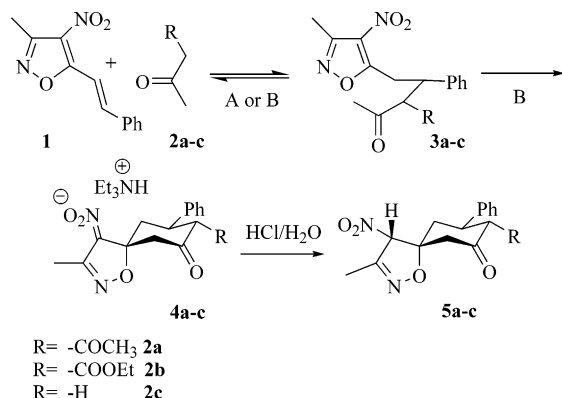


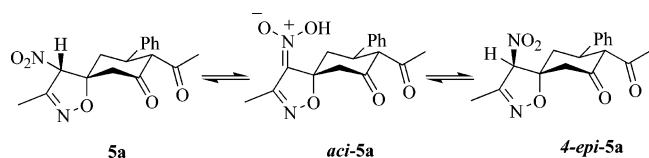
FIGURE 1. Spiroisoxazolines possessing biological activity.

SCHEME 1. Reaction of 1 with Bisenzolizable Compounds 2a–c



four stereogenic centers are formed with complete control of the relative stereochemistry. The diastereoisomer obtained is the most thermodynamically stable, holding the sterically demanding groups in the equatorial positions. Although **5a–c** were obtained as a single diastereoisomer in the solid state, when dissolved, compounds **5a–c** underwent a rapid equilibration to form two diastereoisomers in solution (Scheme 2).⁹

SCHEME 2. Behavior of Compounds 5a in Solution



This behavior is usual for aliphatic nitroalkanes which establish an equilibrium with their *aci* form in solution.¹⁰ Therefore, we obtained a ¹H NMR spectrum of compounds **5a–p** (Table 1) as a single diastereoisomer only

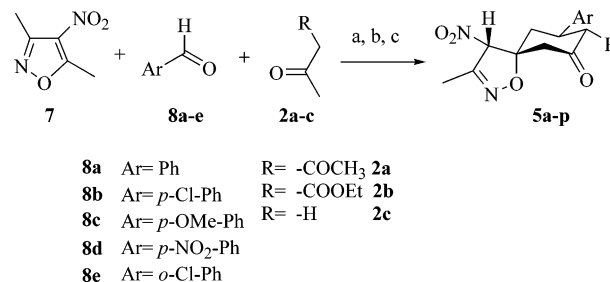
(9) **5a** and *4-epi-5a* were identified by NOE experiments. Significant enhancement was observed between CHNO₂ and OCCH_{ax}H_{eq}C=O in **5a**.

(10) Turnbull, D.; Maron, S. H. *J. Am. Chem. Soc.* **1943**, *65*, 212.

when **5a–p** were dissolved in CD₃COCD₃ or CDCl₃ and the spectrum was rapidly acquired. Typically, a solution of 8–10 mg of **5a** in 0.6 mL of CD₃COCD₃ required 4 min to epimerize to a 1:1 ratio of **5a** and *4-epi-5a* (Scheme 2). Because of the long acquisition times required, the ¹³C NMR of compounds **5a–p** displayed a 1:1 mixture of **5** and *4-epi-5* diastereoisomers.¹¹

We report now a new one-pot three-component procedure (MCR-3) which allows the preparation of spiroisoxazolines **5a–p** (Scheme 3 and Table 1) in a modular fashion and from commercially available materials. Mul-

SCHEME 3. One-Pot Procedure To Prepare Spiroisoxazolines^a



^a Conditions and reagents: (a) **7**, **8a–c** (1 equiv), piperidine (0.1 equiv), ethanol, 60 °C, 2 h; (b) **2a–c** (2 equiv), piperidine (1.9 equiv), 60 °C, 6 h; (c) HCl (dil).

ticomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.¹² In these procedures a number of building blocks come together in a single reaction vessel to form a new product in which each individual component is contained. Therefore, in MCRs, a high degree of molecular diversity can be introduced by variation of a single component at a time. Considering that rapidity and diversity are key features in modern drug discovery, it becomes clear that MCR strategies offer significant advantages over traditional

(11) ¹H NMR studies showing the epimerization of **5a** to *4-epi-5a* are included in the Supporting Information.

(12) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. Ramon, D. J.; Yuss, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.

linear-type syntheses, especially when designed to rely on readily available materials.

Our approach to the development of diversity-oriented syntheses is based on the generation of building blocks that contain multiple functionalities which could be selectively reacted.^{8,13,14} We worked on the hypothesis that a product containing a number of functionalities m which could be selectively reacted in a number of n directions will generate diversity in $D = mn$ directions.

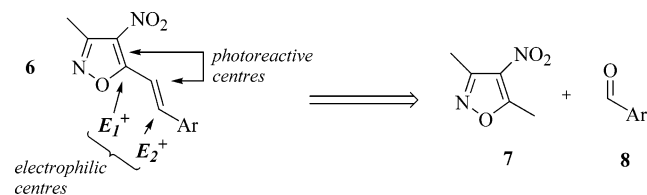


FIGURE 2. Polyfunctional scaffold: 5-styryl-4-nitroisoxazoles **6**.

In this respect, 3-methyl-4-nitro-5-styrylisoxazoles **6** (Figure 2) represent a class of polyfunctional scaffolds which hold great potential for the generation of diversity. For example, in **6** two electrophilic centers are available that can each be reacted independently. Enolates, which are stabilized soft nucleophiles, react selectively at the soft electrophilic center E_2^+ ,⁸ whereas hard nucleophiles such as $-\text{OH}$ react exclusively at the hard electrophilic center E_1^+ ; for example, it was shown that treatment of **6** with NaOH generated cinnamic acids.¹⁵ The photochemical behavior of **6** has also been studied extensively, and it was shown that cyclobutanes could be accessed by irradiation of **6**.¹⁶ Photochemistry thus enhances the range of directions in which diversity can be generated from **6**. Additional practical features of **6** are their stability and their ease of generation from commercially available materials 3,5-dimethyl-4-nitroisoxazole (**7**) and an aromatic aldehyde (**8**) (Figure 2) by a condensation reaction.

Considering that tandem syntheses involving sequential Knoevenagel and Michael processes have been extensively reported,¹⁷ we anticipated that spiroisoxazolines **5** could be prepared through a multicomponent procedure in which **6** was first generated from **7** and **8** and then reacted in situ with **2a–c** (Figure 3).

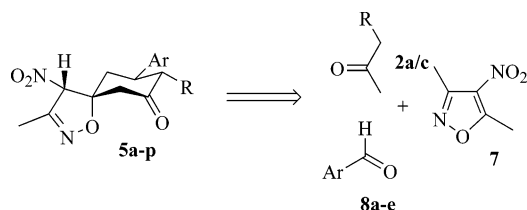


FIGURE 3. One-pot synthesis of spiroisoxazolines **5a–p**.

The following findings were pivotal to the establishment of a one-pot procedure. The preparation of 4-nitro-5-styrylisoxazoles from **7** and **8** has previously been reported using large amounts of triethylamine or piperidine base.¹⁸ However, we found that only a limited

amount of piperidine (0.1 equiv) was required for the condensation of components **7** and **8** and that using the catalyst base in restricted amounts led to improved yields and increased the purity of the products. We also observed that secondary amines such as piperidine, pyrrolidine, or morpholine were better catalysts than tertiary amines for the synthesis of **6** and for the following Michael reactions (Scheme 1). Finally, in the reaction of **1** with **2a–c** only 0.1 equiv of piperidine was required to obtain adducts **3a–c** in good yields, and just 2 equiv of piperidine was required to convert **1** to spiroisoxazolines **5a–c**.

These findings defined a set of optimized conditions that were used to prepare spiroisoxazolines **5a–p** in one pot and in excellent isolated yields (Scheme 3 and Table 1). Typically, (condition a, Scheme 3) equimolar amounts

TABLE 1. Yields of Spiroisoxazolines **5a–p**

entry	product	Ar	R	yield (%)
1	5a	Ph–	–COCH ₃	83
2	5b	Ph–	–CO ₂ Et	71
3	5c	Ph–	–H	84
4	5d	<i>p</i> -NO ₂ Ph–	–COCH ₃	83
5	5e	<i>p</i> -NO ₂ Ph–	–CO ₂ Et	71
6	5f	<i>p</i> -NO ₂ Ph–	–H	78
7	5g	<i>p</i> -ClPh–	–COCH ₃	80
8	5h	<i>p</i> -ClPh–	–CO ₂ Et	69
9	5i	<i>p</i> -ClPh–	–H	86
10	5k	<i>o</i> -ClPh–	–COCH ₃	65 ^a
11	5l	<i>o</i> -ClPh–	–CO ₂ Et	59
12	5m	<i>o</i> -ClPh–	–H	68
13	5n	<i>p</i> -OCH ₃ Ph–	–COCH ₃	85
14	5o	<i>p</i> -OCH ₃ Ph–	–CO ₂ Et	72
15	5p	<i>p</i> -OCH ₃ Ph–	–H	77

^a Obtained as the 8-enolic form.

of **7** and aromatic aldehyde **8a–e** were reacted in the presence of piperidine (0.1 equiv) in ethanol (2 h at 60 °C), (condition b, Scheme 3), a moderate excess (2 equiv) of **2a–c** was added to the reaction mixture together with a further amount of piperidine (1.9 equiv) and the reaction mixture was heated (6 h at 60 °C), and (condition c, Scheme 3) evaporation of the solvent and workup with aqueous dilute hydrochloric acid gave compounds **5a–p** without the need for column chromatography. This ease of purification complements the one-pot procedure, making this methodology facile, practical, and rapid to execute.

As a means of expanding the range of chemically diverse species available from **5**, we developed a similar one-pot procedure that could be used to access adducts **3a–m** (Scheme 4 and Table 2). Adducts **3a–m** constitute a class of polyfunctional scaffolds themselves. Compounds **3a–m** contain a ketone, a β -diketone, or a β -ketoester

(15) Sarti-Fantoni, P.; Donati, D.; De Sio, F.; Moneti, G. *J. Heterocycl. Chem.* **1980**, *17*, 1643. Baracchi, A.; Chimichi, S.; De Sio, F.; Donati, D.; Nesi, R.; Sarti-Fantoni, P.; Torroba, T. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 487.

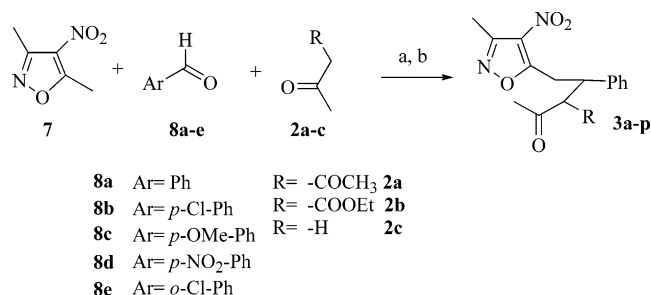
(16) Donati, D.; Fiorenza, M.; Moschi, E.; Sarti-Fantoni, P. *J. Heterocycl. Chem.* **1977**, *14*, 951. Baracchi, A.; Chimichi, S.; De Sio, F.; Donati, D.; Nesi, R.; Sarti-Fantoni, P.; Torroba, T. *Heterocycles* **1986**, *24*, 2863.

(17) List B. *Synlett* **2001**, *11*, 1675.

(18) Kochetkov, N. K.; Sokolov, S. D.; Luboschnikova, V. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1962**, *32*, 1763. Quilico, C.; Musante, A. *Gazz. Chim. Ital.* **1942**, *72*, 399.

(13) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Rathmell, R. E. *Tetrahedron* **2003**, *59*, 2197.

(14) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. *Org. Chem.* **2005**, *70*, 3307.

SCHEME 4. One-Pot Synthesis of Adducts 3a–p^a

^a Conditions and reagents: (a) **7**, **8a–e** (1 equiv), piperidine (0.1 equiv), ethanol, 60 °C, 2 h; (b) **2a–c** (1.2 equiv), 60 °C, 6 h.

functionality together with a 4-nitroisoxazole core. Considering that carbonyl-containing compounds¹⁹ and the 4-nitroisoxazole core²⁰ were shown to possess a wide range of different reactivities, it is easy to anticipate that diversity could stem from **3a–m** in a wide number of directions.

TABLE 2. Yields of Michael Adducts 3a–p

entry	product	Ar	R	yield (%)
1	3a	Ph–	–COCH ₃	84
2	3b	Ph–	–CO ₂ Et	69
3	3c	Ph–	–H	82
4	3d	<i>p</i> -NO ₂ Ph–	–COCH ₃	82
5	3e	<i>p</i> -NO ₂ Ph–	–CO ₂ Et	74 ^a
6	3f	<i>p</i> -NO ₂ Ph–	–H	80
7	3g	<i>p</i> -ClPh–	–COCH ₃	71
8	3h	<i>p</i> -ClPh–	–CO ₂ Et	78
9	3i	<i>p</i> -ClPh–	–H	81
10	3k	<i>o</i> -ClPh–	–COCH ₃	62
11	3l	<i>o</i> -ClPh–	–CO ₂ Et	52 ^a
12	3m	<i>o</i> -ClPh–	–H	72
13		<i>p</i> -OCH ₃ Ph–	–COCH ₃	<i>b</i>
14		<i>p</i> -OCH ₃ Ph–	–CO ₂ Et	<i>b</i>
15		<i>p</i> -OCH ₃ Ph–	–H	<i>b</i>

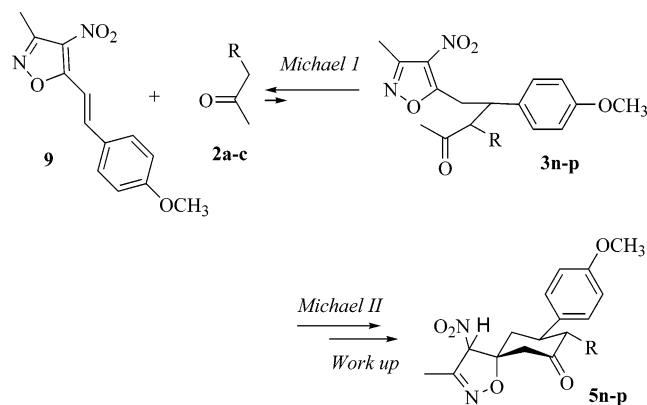
^a Obtained as a 1:1 mixture of diastereoisomers. ^b A 5–8% yield of the corresponding spiroisoxazolines **5n–p** was isolated together with a 75–85% yield of **9**.

Similarly, (condition a, Scheme 4) equimolar amounts of **7** and aromatic aldehyde **8a–e** were reacted in the presence of piperidine (0.1 equiv) in ethanol (2 h at 60 °C), and (condition b, Scheme 4) a moderate excess (1.2 equiv) of **2a–c** was added and the reaction mixture was heated (6 h at 60 °C). Compounds **3a–m** were isolated in good yields; however, we could not isolate compounds **3n–p** (Table 2, entries 13–15). These experiments furnished compounds **5n–p** in only 5–8% yields together with a 70–75% yield of 3-methyl-4-nitro-5-(4-methoxyphenyl)ethenylisoxazole (**9**) (Scheme 5).

We explained this result as follows (Scheme 5). The first reaction (Michael I, Scheme 5) is a reversible process, and in the case of a less effective acceptor such as *p*-OCH₃-substituted styrylisoxazole **9**, the equilibrium for this step is shifted toward the reagents. On the contrary, the second reaction (Michael II, Scheme 5) is an irreversible process, and in the presence of a suitable amount of piperidine base, the final products **5n–p** are formed effectively.

In light of these results, the 3-MCR procedure we have developed to prepare spiroisoxazolines could be classified

SCHEME 5.



as a type II MCR.²¹ In a type II MCR, a final product D is irreversibly formed from an intermediate compound C, which is in equilibrium with its precursors A and B, which is analogous to our case.

In conclusion, we have developed an effective methodology for the assembly of title compounds from commercially available materials. This new methodology is modular, and benefits from a simple method of purification which does not require chromatography. We also have established a modular one-pot approach to the preparation of heteroaryl β -diketones, heteroaryl ketones, and heteroaryl β -ketoesters. Spiroisoxazolines are known to possess a wide range of biological activities, and also in **5a–p**, a number of functionalities are present that will allow a further development of chemical diversity. Similar considerations are valid for adducts **3a–m**.

Experimental Section

General Procedure for the Preparation of Compounds 5a–p (Table 1). To a stirred solution of **7** (426 mg, 3 mmol) in ethanol (10 mL) were added piperidine (26 mg, 0.3 mmol, 0.1 equiv) and an aromatic aldehyde (**8a–e**) (3 mmol, 1 equiv). The resulting solution was reacted at 60 °C for 2 h, before ketone **2a–c** (6 mmol, 2 equiv) was added together with a further amount of piperidine (485 mg, 5.7 mmol, 1.9 equiv). The reaction mixture was heated at 60 °C for 6 h and then allowed to cool at room temperature and the solvent removed in vacuo. The yellow oil so obtained was treated with water (100 mL) and extracted with diethyl ether (2 \times 25 mL). The organic layer was discarded and the aqueous phase made acidic (pH \approx 1–2) by addition of 1 M hydrochloric acid and extracted with diethyl ether (2 \times 50 mL). This second organic layer was dried over MgSO₄, filtered, and evaporated to yield crude spiroisoxazolines **5a–p** as colorless solids, which were recrystallized from ethanol.

Data for 8-acetyl-3-methyl-4-nitro-9-phenyl-1-oxa-2-azaspiro[4.5]dec-2-en-7-one (5a): colorless solid (820 mg, 83% yield); mp 170–1 °C (ethanol); ν_{\max} (film)/cm⁻¹ 1710s, 1702s, 1575m; ¹H NMR (400 MHz, CD₃COCD₃) δ 7.41–7.23 (5H, m), 6.02 (1H, s), 4.43 (1H, d, *J* = 12 Hz), 3.79 (1H, td, *J* = 12 Hz, *J* = 4 Hz), 3.24 (1H, d, *J* = 14 Hz), 2.73 (1H, dd, *J* = 12 Hz, *J* = 2.5 Hz), 2.63 (1H, t, *J* = 12 Hz), 2.02 (3H, s), 1.88 (3H, s), 1.89 (1H, ddd, *J* = 12 Hz, *J* = 4 Hz, *J* = 2.5 Hz); ¹³C NMR (400 MHz, CD₃COCD₃) (*4-epi-5a*) δ 7.41–7.23 (5H, m), 5.88 (1H, s), 4.43 (1H, d, *J* = 12 Hz), 3.79 (1H, td, *J* = 12 Hz, *J* = 4 Hz), 3.28 (1H, d, *J* = 14 Hz), 2.52 (1H, t, *J* = 12 Hz), 2.37 (1H, dd, *J* = 12 Hz, *J* = 2.5 Hz), 2.18 (1H, ddd, *J* = 12 Hz, *J* = 4 Hz, *J* = 2.5 Hz), 2.02 (3H, s), 1.88 (3H, s); ¹³C NMR (80 MHz, CD₃COCD₃) δ 202.7, 201.9, 201.8, 151.2, 151.0, 141.2, 128.3, 127.8, 126.9, 126.8, 97.8, 97.5, 88.1, 66.5, 66.4, 48.6, 44.6, 41.0, 37.5, 36.9, 35.9, 29.8, 10.7; MS *m/z* 331 (100,

MH⁺). Anal. Calcd for C₁₇H₁₈N₂O₅: C, 61.81; H, 5.45; N, 8.48. Found: C, 61.77; H, 5.48; N, 8.21.

Data for 3-methyl-4-nitro-7-oxo-9-phenyl-1-oxa-2-aza-spiro[4.5]dec-2-ene-8-carboxylic acid ethyl ester (5b): colorless solid (765 mg, 71% yield); mp 148–9 °C (ethanol); ν_{\max} (film)/cm⁻¹ 1725s, 1570s; ¹H NMR (200 MHz, CDCl₃) δ 7.32–7.21 (5H, m), 5.36 (1H, s), 4.05 (2H, q, *J* = 7 Hz), 3.96–3.81 (1H, m), 3.71 (1H, d, *J* = 13 Hz), 2.81 (1H, d, *J* = 15 Hz), 2.70 (1H, dd, *J* = 15 Hz, *J* = 2 Hz), 2.32–2.12 (2H, m), 2.13 (3H, s), 1.06 (3H, t, *J* = 7 Hz); ¹³C NMR (80 MHz, CD₃COCD₃) δ 199.5, 167.2, 150.4, 150.2, 140.8, 140.7, 128.2, 127.0, 126.8, 97.9, 97.6, 88.1, 61.7, 61.3, 59.7, 48.1, 43.5, 41.7, 41.5, 40.1, 35.4, 12.9, 10.7; HRMS *m/z* found (MH⁺) 361.1399, C₁₈H₂₁N₂O₆ requires 361.1400; MS *m/z* 361 (95, MH⁺).

Data for 3-methyl-4-nitro-9-phenyl-1-oxa-2-azaspiro[4.5]dec-2-en-7-one (5c): colorless solid (728 mg, 84% yield); mp 141–2 °C (ethanol); ν_{\max} (film)/cm⁻¹ 1720s, 1570s; ¹H NMR (200 MHz, CD₃COCD₃) δ 7.15–6.99 (5H, m), 5.74 (1H, s), 3.15 (1H, tt, *J* = 14 Hz, *J* = 4 Hz), 2.92–2.60 (2H, m), 2.42–2.03 (3H, m), 1.90 (3H, s), 1.83–1.61 (1H, m); ¹³C NMR (80 MHz, CD₃COCD₃) 205.6, 204.2, 150.4, 150.1, 143.6, 142.9, 128.1, 127.6, 127.2, 126.7, 126.1, 98.4, 98.1, 89.7, 48.6, 47.1, 46.9, 43.8, 40.5, 39.0, 38.7, 35.7, 10.7; HRMS *m/z* found (MH⁺) 289.1189, C₁₅H₁₇N₂O₄ requires 289.1188; MS *m/z* 289 (95, MH⁺).

General Procedure for the Preparation of Compounds 3a–m (Table 3). To a solution of **7** (426 mg, 3 mmol) in ethanol (10 mL) were added piperidine (26 mg, 0.3 mmol, 0.1 equiv) and an aromatic aldehyde (**8a–e**) (3 mmol, 1 equiv). The reaction mixture was reacted at 60 °C for 2 h, then ketone **2a–c** (3.6 mmol, 1.2 equiv) was added, and the reaction was further reacted for 6 h at the same temperature. After this time, the reaction mixture was allowed to reach room temperature, the solvent removed in vacuo, and the oil so obtained purified by flash chromatography.

Data for 3-[2-(3-methyl-4-nitroisoxazol-5-yl)-1-phenylethyl]pentane-2,4-dione (3a): colorless solid (831 mg, 84% yield); *R*_f = 0.2 (ethyl acetate:petroleum ether = 1:5); mp 121–2 °C (ethanol); ν_{\max} (film)/cm⁻¹ 1705s, 1600s, 1520m; ¹H NMR (400 MHz, CDCl₃) δ 7.16–6.98 (5H, m), 4.20 (1H, d, *J* = 12 Hz), 4.10 (1H, m), 3.46 (1H, dd, *J* = 14 Hz, *J* = 9 Hz), 3.26 (1H, dd, *J* = 14 Hz, *J* = 5 Hz), 2.33 (3H, s), 2.20 (3H, s), 1.75

(3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 202.1, 201.7, 171.8, 155.4, 138.0, 131.0, 129.0, 128.0, 127.7, 74.7, 42.6, 32.3, 29.6, 29.4, 11.5; HRMS *m/z* found (MH⁺) 331.1295, C₁₇H₁₉N₂O₅ requires 331.1294; MS *m/z* 331 (100, MH⁺).

Data for 2-acetyl-4-(3-methyl-4-nitroisoxazol-5-yl)-3-phenylbutyric acid ethyl ester (3b): colorless solid (745 mg, 69% yield); *R*_f = 0.4 (ethyl acetate:petroleum ether = 1:4); mp 84–5 °C (ethanol); ν_{\max} (film)/cm⁻¹ 1726s (C=O), 1601s (1s), 1525m (NO₂); ¹H NMR (200 MHz, CDCl₃) δ 7.18–7.02 (5H, m), 4.01–3.90 (2H, m), 3.81 (2H, q, *J* = 7 Hz), 3.55 (1H, dd, *J* = 14 Hz, *J* = 7 Hz), 3.38 (1H, dd, *J* = 14 Hz, *J* = 5 Hz), 2.36 (3H, s), 2.20 (3H, s), 0.85 (3H, t, *J* = 7 Hz); ¹³C NMR (80 MHz, CDCl₃) δ 201.0, 172.2, 167.7, 155.3, 138.5, 130.5, 128.9, 128.6, 127.8, 65.4, 61.5, 42.6, 31.9, 30.0, 14.7, 11.4; HRMS *m/z* found (MH⁺) 361.1398, C₁₈H₂₁N₂O₆ requires 361.1399; MS *m/z* 361 (100, MH⁺).

Data for 5-(3-methyl-4-nitroisoxazol-5-yl)-4-phenylpentan-2-one (3c): colorless oil (708 mg, 82% yield); *R*_f = 0.4 (ethyl acetate:petroleum ether = 1:5); ν_{\max} (film)/cm⁻¹ 1709s (C=O), 1600m (1s), 1575s (NO₂); ¹H NMR (400 MHz, CDCl₃) δ 7.29–7.19 (5H, m), 3.84 (1H, quintet, *J* = 7 Hz), 3.60 (1H, dd, *J* = 14 Hz, *J* = 7 Hz), 3.47 (1H, dd, *J* = 14 Hz, *J* = 7 Hz), 2.96 (1H, dd, *J* = 17 Hz, *J* = 7 Hz), 2.88 (1H, dd, *J* = 17 Hz, *J* = 7 Hz), 2.50 (3H, s), 2.10 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 205.6, 172.5, 154.9, 141.2, 132.6, 130.1, 128.4, 126.6, 48.7, 38.5, 33.4, 30.0, 11.2; HRMS *m/z* found (MH⁺) 289.1189, C₁₅H₁₇N₂O₄ requires 289.1188; MS *m/z* 289 (100, MH⁺).

Acknowledgment. We acknowledge the Royal Society of Chemistry for a grant to M.F.A.A. and the RCSI Research Committee and PTRLI cycle III for a grant to E.F.D.

Supporting Information Available: General experimental procedures, spectroscopic data for compounds **5d–p** and **3d–m**, ¹H NMR spectra showing the epimerization of **5a** to 4-*epi*-**5a**, ¹H NMR spectra of compounds **5a–p** and **3a–m**, ¹H and ¹³C NMR peak assignments for **5a** and 4-*epi*-**5a**, ¹H–¹H correlation and ¹H–¹³C correlation spectra of compound **5a**, and NOE experiments for assigning the identity of **5a** and 4-*epi*-**5a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051181W

(19) Kel'in, A. V.; Maioli, A. *Curr. Org. Chem.* **2003**, *7*, 1855.

(20) Kashima, C. *Heterocycles* **1979**, *12*, 1343.

(21) Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 499.