



Knoevenagel condensation of cyclic ketones with benzoylacetonitrile and *N,N'*-dimethylbarbituric acid. Application of sterically hindered condensation products in the synthesis of spiro and dispiropyrans by hetero-Diels–Alder reactions

Aleksandra Pałasz^{a,*}, Tadeusz Pałasz^b

^a Department of Organic Chemistry, Jagiellonian University, Ingardena 3 St, 30-060 Kraków, Poland

^b Marian Smoluchowski Institute of Physics, Jagiellonian University, Reymonta 4 St, 30-059 Kraków, Poland

ARTICLE INFO

Article history:

Received 20 September 2010

Received in revised form 28 November 2010

Accepted 20 December 2010

Available online 25 December 2010

Keywords:

Spiro compounds

Hetero-Diels–Alder reactions

1-Oxa-1,3-butadienes

Uracils

ABSTRACT

Inverse-electron demand Diels–Alder cycloadditions of sterically hindered cycloalkylidene derivatives of benzoylacetonitrile and *N,N'*-dimethylbarbituric acid with enol ethers, cyclic enol ethers and also sterically hindered cycloalkylidenecycloalkanes were investigated. New spiro, dispirodihydropyrans, spirouracils, and dispirofuracils were obtained. To confirm the experimental results, frontier orbital HOMO and LUMO energies of heterodienes and dienophiles were calculated by semi-empirical AM1, PM3 methods and ab initio Hartree–Fock calculations.

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1. Introduction

Cycloaddition reactions provide rapid and elegant methods for the construction of mono- and polycyclic systems. The development of new cycloreactants is a continuous challenge in the field of pericyclic reactions. The use of hetero-substituted diene and dienophiles is of specific interest for the application of Diels–Alder cycloadditions toward natural and biologically active product synthesis.¹ Reports in this area mainly concern the use of heterodienes with different substituents, but none have reported the use of sterically hindered cycloalkylidene derivatives of heterodienes. Pyran derivatives are common structural subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids.¹ Also fused uracils, such as pyrano[2,3-*d*]pyrimidines, pyrido[2,3-*d*]pyrimidines, pyrazo[3,4-*d*]pyrimidines or pyrimido[4,5-*d*]pyrimidines are reported to have a wide range of biological activities, such as antiallergic, anti-hypertensive, cardiotonic, bronchodilator, antibronchitic or antitumor activity.² The preparation of the mentioned compounds containing a pyran and an uracil ring poses significant synthetic challenges. 3,4-Dihydro-2*H*-pyrans can be efficiently synthesized by an inverse-electron-demand hetero-Diels–Alder (HDA) reactions of

α,β -unsaturated carbonyl compounds representing an 1-oxa-1,3-butadiene system with enol ethers.³ It was stated that introducing an electron-withdrawing group in the 1-oxa-1,3-diene system can enhance their reactivity.⁴ In recent work, we have shown that intermolecular and intramolecular HDA reactions are a powerful tool in 2*H*-pyran and polycyclic 2*H*-pyran derivatives synthesis.⁵ In this paper, the first examples of an inverse-electron demand hetero-Diels–Alder reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles and 5-cycloalkylidene-1,3-dimethyl-pyrimidine-2,4,6-triones as the heterodienes are described.

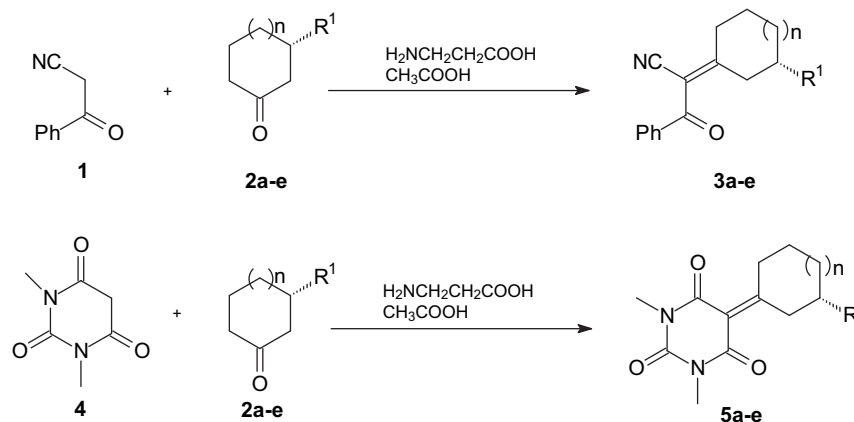
The Knoevenagel condensation is a common synthetic method for alkene formation.⁶ The Knoevenagel reaction of various aromatic and heteroaromatic aldehydes with active methylene compounds, such as barbituric acids, Meldrum's acid, dimedone, malononitrile, ethyl cyanoacetate have been widely used in synthesis of arylidene derivatives. The reactions with aromatic aldehydes are usually catalyzed by bases or acids. Amines, such as piperidine or triethylamine, sodium ethoxide, acetic acid, or mixtures of acetic acid and sulfuric acid,⁷ acetic acid and piperidine,⁸ ammonium acetate and acetic acid⁹ have also been successfully used as catalyst. Lewis acids, surfactants have also been employed to catalyze the condensations reactions.¹⁰ However, reports describing analogous procedures for ketones are rare, because ketones have low reactivity in the condensations with CH acids. Soto et al. described Knoevenagel condensations of the cycloalkanones with an aryl β -ketonitrile at reflux in benzene or toluene in the

* Corresponding author. E-mail addresses: palasz@chemia.uj.edu.pl (A. Pałasz), tadeusz.palasz@uj.edu.pl (T. Pałasz).

presence of a mixture of piperidine and caproic acid as the catalyst.¹¹ The same reactions were carried out with using of mixture of β -alanine and acetic acid as catalyst.¹²

2. Results and discussion

The aim of the work was to investigate if 1-oxa-1,3-butadienes that are sterically hindered at the C-4 carbon, for example, cycloalkylidene derivatives of benzoylacetonitrile **1** or *N,N'*-dimethylbarbituric acid **4** can act as active heterodienes in hetero-Diels–Alder reactions in synthesis of spiro and dispirodihydropyrans. First, potential heterodienes with cycloalkylidene moiety were synthesized and in the second step their reactions with enol ethers and cyclic enol ether were conducted. Heterodienes **3a–e** and **5a–e** were synthesized by Knoevenagel condensation of benzoylacetonitrile **1** or *N,N'*-dimethylbarbituric acid **4** with appropriate cycloalkanone **2a–e** (enantiomerically pure (*R*)-(+)-3-methylcyclohexanone **2e** has been used) by refluxing in toluene or xylene for 4–6 h in the presence of β -alanine and acetic acid as catalyst according to a procedure described in ref. 12b. The progress of the reactions was monitored by TLC. Compounds **3a–e** and **5a–e** were obtained in good 77–87% yields (Scheme 1, Table 1).



Scheme 1. Knoevenagel condensations of benzoylacetonitrile **1** or *N,N'*-dimethylbarbituric acid **4** with cyclic ketones **2a–e**.

Table 1
Synthesis of cycloalkylidene derivatives **3a–e** and **5a–e** by Knoevenagel condensation

Methylene compound	Cyclic ketone	<i>n</i>	R ¹	Knoevenagel condensation product	Reaction time/h ^a	Yield %
1	2a	1	H	3a	5 (t)	87
1	2b	0	H	3b	4 (t)	86
1	2c	2	H	3c	5 (t)	84
1	2d	3	H	3d	6 (t)	82
1	2e	1	CH ₃	3e	6 (t)	81
4	2a	1	H	5a	5 (x)	82
4	2b	0	H	5b	4 (x)	87
4	2c	2	H	5c	5 (x)	86
4	2d	3	H	5d	5 (x)	86
4	2e	1	CH ₃	5e	6 (x)	77

^a Reaction mixture was heated to reflux in toluene (t) or xylene (x).

The cycloaddition reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles **3a–e** or 5-cycloalkylidene-1,3-dimethylpyrimidine-2,4,6-triones **5a–e** with enol ethers **6a–c** were performed in toluene solution at 110 °C for 24 h and the spiropyrans **7a–g** and **8a–e** were obtained in good 78–93% yields (Scheme 2, Table 2). The progress of the reactions was monitored by TLC.

Compounds **7a–g** and **8a–e** were characterized by ¹H, ¹³C NMR, IR, mass spectra, and elemental analysis. The ¹H and ¹³C signal assignments were confirmed by two-dimensional NMR COSY and HETCOR spectra. The configuration of the C-2' substituents of spiropyrans **7a–g** or C-7' of **8a–e** was assigned on the basis of ¹H NMR spectra. They were deduced from the chemical shift values and coupling constants of the protons attached to C-2' or C-7' of the dihydropyran ring that exists in a half-chair conformation¹³ (Table 3).

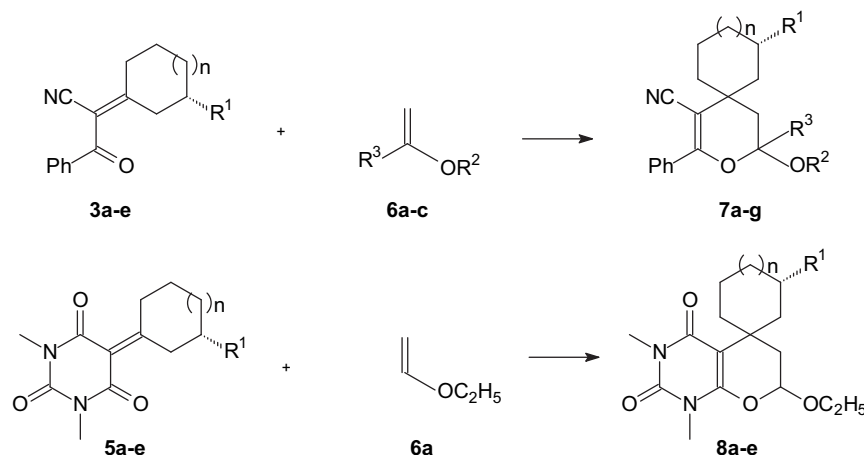
In the ¹H NMR spectra of spiropyrans **7a–g** the signals of 2'-H appear as a doublet of doublets at δ =5.13–5.28 ppm with coupling constants (³*J*=7.2–8.4 and 2.4–3.0 Hz) due to coupling with two protons at C-3' (Table 3). Thus, 2'-H is in the *axial* position and the alkoxy group occupies the *equatorial* position. (Fig. 1). The ¹H NMR spectra of **8a–e** reveal the signals of proton 7'-H as a doublet of doublets at δ =4.99–5.20 ppm with coupling constants (³*J*=8.1–8.7 and 2.1–2.4 Hz) (Table 3). Thus, 7'-H is in the *axial* position and the alkoxy group is *equatorial* (Fig. 1).

For cycloadditions of compounds **3e** or **5e** with ether **6a** high diastereoselectivity was observed because products **7g** and **8e** were obtained each as one diastereoisomer from four diastereoisomers presented on the Fig. 2. Analysis of two-dimensional NMR COSY,

NOESY, and HETCOR spectra compounds **7g** and **8e** does not allow the configuration to be assigned unambiguously. It was impossible to determinate the crystallographic structure of compounds **7g** and **8e** because they are oils.

Although only one diastereoisomer of the compounds **7g** or **8e** was obtained in Diels–Alder reactions, the formation of the minor isomers has not been formally excluded. Therefore, acetals **7g** and **8e** were submitted to the action of Lewis acid to equilibrate one isomer to another isomer. The diastereoisomers of the compounds **7g** and **8e** obtained in the cycloaddition reactions were mixed with boron trifluoride diethyl etherate BF₃Et₂O. In both examined cases the mixtures of the diastereoisomer submitted to the action of Lewis acid (diastereoisomer **A**) and a new diastereoisomer (diastereoisomer **B**) was obtained (**A/B**=1:2.3 for **7g**, **A/B**=1:1.9 for **8e**) after 24 h at room temperature. The ratios of isomers **A/B** were determined on the basis of ¹H NMR spectra of crude mixtures after isomerization reactions.

Encouraged by previous presented results, we next embarked on the inverse-electron-demand hetero-Diels–Alder reactions between cycloalkylidene derivatives **3** or **5** and cyclic enol ether 2-methylenetetrahydropyran **9**. The compound **9** was prepared according to the literature with a yield of 69% from 2-(chloromethyl)tetrahydropyran¹⁴ that was prepared from tetrahydropyran-2-methanol.¹⁵ The cycloaddition reactions of **3a**, **3e**, **5a**,



Scheme 2. Hetero-Diels–Alder reactions of cycloalkylidene derivatives **3a–e** and **5a–e** with enol ethers **6a–c**.

Table 2
Synthesis of spirocycloadducts **7a–g** and **8a–e** by Diels–Alder reactions

Diene	<i>n</i>	R ¹	Enol ether	R ²	R ³	Spirocycloadduct	Yield % ^a
3a	1	H	6a	C ₂ H ₅	H	7a	89
3a	1	H	6b	<i>i</i> -Bu	H	7b	91
3a	1	H	6c	CH ₃	CH ₃	7c	84
3b	0	H	6a	C ₂ H ₅	H	7d	87
3c	2	H	6a	C ₂ H ₅	H	7e	86
3d	3	H	6a	C ₂ H ₅	H	7f	83
3e	1	CH ₃	6a	C ₂ H ₅	H	7g	87
5a	1	H	6a	C ₂ H ₅	H	8a	79
5b	0	H	6a	C ₂ H ₅	H	8b	93
5c	2	H	6a	C ₂ H ₅	H	8c	91
5d	3	H	6a	C ₂ H ₅	H	8d	88
5e	1	CH ₃	6a	C ₂ H ₅	H	8e	78

^a Isolated yields after column chromatography.

Table 3
Signals of protons 2'-H and 7'-H in ¹H NMR spectra of spirodihydropyrans **7a–g** and **8a–e**

7	dd 2'-H	8	dd 7'-H
	δ (ppm)		δ (ppm)
	$J_{3'ax,2'}/J_{3'eq,2'}$ (Hz)		$J_{6'ax,7'}/J_{6'eq,7'}$ (Hz)
7a	5.13	8a	5.13
	8.1/2.4		8.4/2.1
7b	5.13	8b	5.08
	7.2/2.7		8.1/2.1
7d	5.14	8c	5.18
	7.8/2.4		8.7/2.1
7e	5.17	8d	5.20
	8.1/2.4		8.7/2.4
7f	5.22	8e	4.99
	8.4/2.7		8.7/2.4
7g	5.28		
	8.4/3.0		

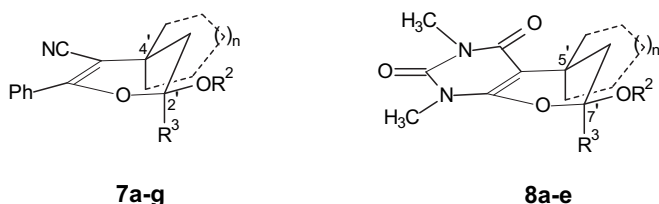


Fig. 1. Preferred configurations and conformations of spirocycloadducts **7a–g** and **8a–e** based on ¹H NMR analysis.

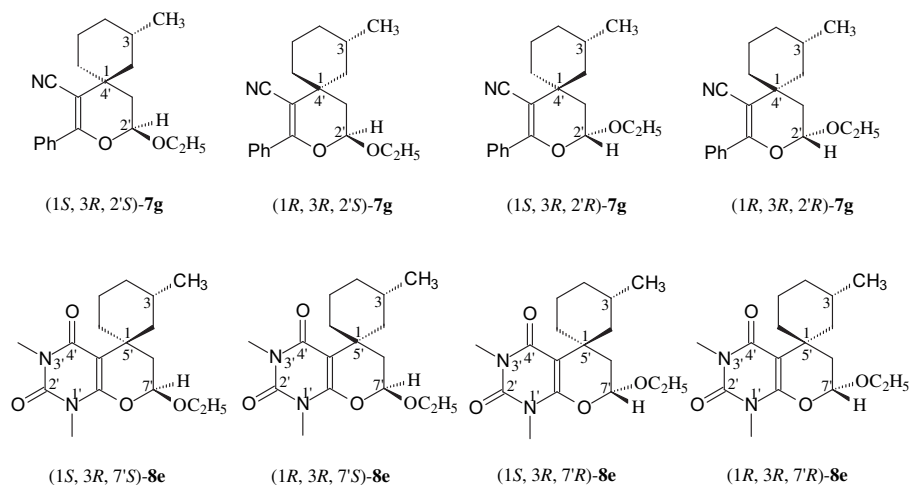
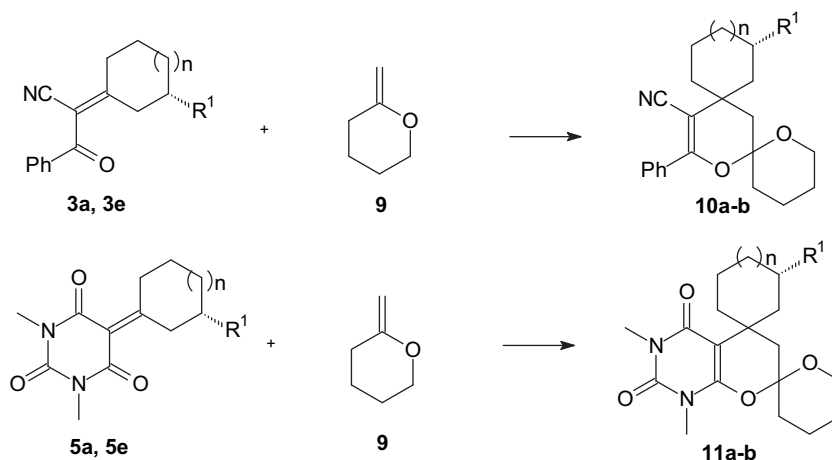
and **5e** with **9** were performed in toluene solution at 110 °C for 24 h and the spirocycloadducts **10a**, **10b**, **11a**, and **11b** were obtained in good 87–93% yields (Scheme 3, Table 4). The progress of the reactions was monitored by TLC using mixture ethyl acetate/pet. ether as an eluent.

Compounds **10a**, **10b**, **11a**, and **11b** were characterized by ¹H, ¹³C NMR, IR, mass spectra, and elemental analysis. ¹H and ¹³C signal assignments were confirmed by two-dimensional NMR COSY and HETCOR spectra.

Only one diastereoisomer was obtained as product in the hetero-Diels–Alder reaction of compounds **3e** or **5e** with cyclic enol ether **9**. Fig. 3 presents possible configurations of dispirocycloadducts diastereoisomers **10b** and **11b**. Again, the analysis of two-dimensional NMR COSY and HETCOR spectra of compounds **10b** and **11b** does not allow the configuration to be unambiguously assigned. There were also problems with preparing of crystals suitable for crystallographic study.

Trispirocycloadducts provide an unusual synthetic challenge, so in the next step, methodology for synthesis of dispirocycloadducts was applied to prepare trispirocycloadducts. The Diels–Alder reactions of cycloalkylidene derivatives **3a** and **5b** with cycloalkylidenecycloalkane **12** and **14** were investigated. Cyclohexylidenecyclohexane **12** and cyclopentylidenecyclopentane **14** were obtained by the new method¹⁶ for reductive coupling of carbonyl compounds to olefins with using of AlCl₃ and Zn as efficient reagents comparable to McMurry's reagent. The reaction mixtures of **3a** with **12** or **5b** with **14** were first heated to reflux in toluene solution for 24 h, but the trispirocycloadducts **13** and **15** were not formed (Scheme 4). The progress of the reactions was monitored by TLC using mixture ethyl acetate/pet. ether as an eluent. The reaction conditions were changed and the reaction mixtures were heated to reflux in xylene solution for 24 h. There was no trace of desired products **13** and **15** so reaction mixtures were heated in xylene solution in the presence of catalytic amounts of the Lewis acids,¹⁷ such as ZnCl₂ or CoCl₂ and no reaction occurred, even after 24 h at reflux.

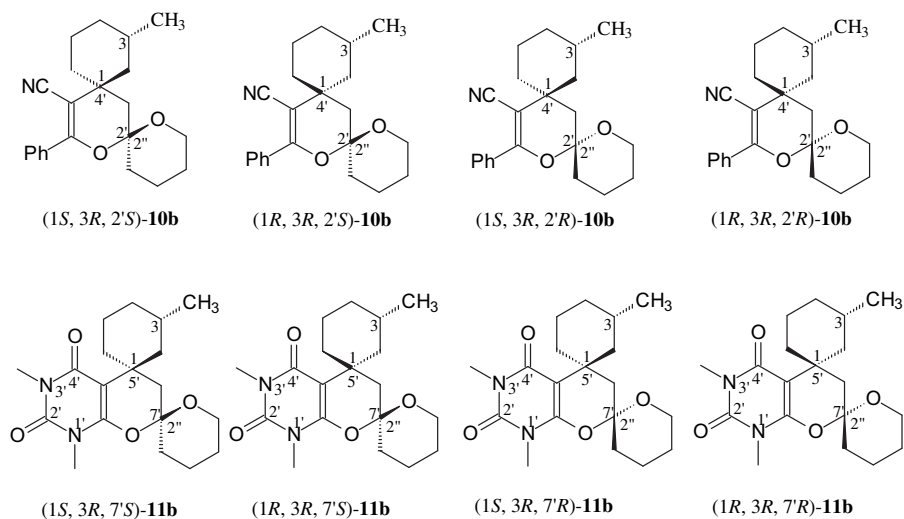
The cycloaddition reactions appear to be under frontier molecular orbital (FMO) control. In order to confirm the experimental results, frontier orbital (HOMO and LUMO) energies of heterodienes **3a**, **3b**, **3e**, **5a**, **5b**, **5e**, and dienophiles **6a**, **9**, **12**, **14** were calculated by semi-empirical AM1 and PM3 methods and ab initio Hartree–Fock calculations using the Gaussian 03 suite of programs. The geometries were fully optimized by PM3 semi-empirical methods and used as the basis for optimization at the Hartree–Fock level using the 3-21G basis set (HF/3-21G). The calculated frontier orbital energies are summarized in Table 5.

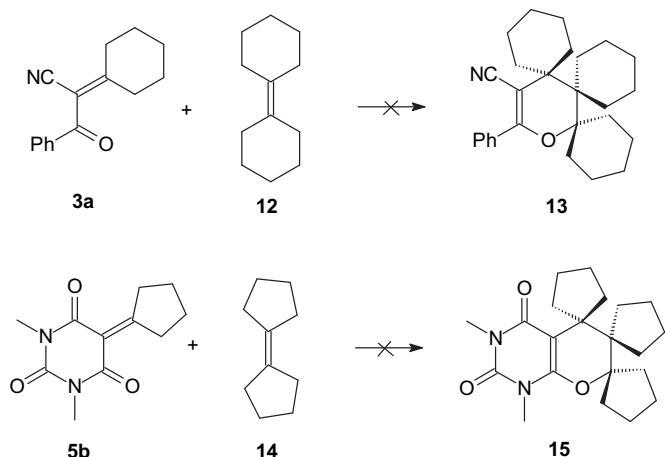
Fig. 2. Diastereoisomers of spiropyrans **7g** and **8e**.Scheme 3. Hetero-Diels–Alder reactions of cycloalkylidene derivatives **3a**, **3e**, **5a**, and **5e** with cyclic enol ether **9**.Table 4
Synthesis of dispiropyrans **10a**, **10b**, **11a**, and **11b** by Diels–Alder reactions

Diene	<i>n</i>	R ¹	Enol ether	Spiropyran	Yield % ^a
3a	1	H	9	10a	93
3e	1	CH ₃	9	10b	91
5a	1	H	9	11a	87
5e	1	CH ₃	9	11b	89

^a Isolated yields after column chromatography.

Investigated cycloadditions are an inverse-electron demand Diels–Alder reactions. In hetero-Diels–Alder reactions with inverse-electron demand, the HOMO orbital of the dienophile (D) overlaps with the LUMO orbital of the heterodiene (H), so energy gaps $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$ were discussed (Table 6). In all the studied cases, the energy gaps for the interaction of the HOMO orbital of heterodiene and the LUMO orbital of the dienophile are higher (from 11.181 to 15.699 eV) than energy differences for the

Fig. 3. Diastereoisomers of dispiropyrans **10b** and **11b**.



Scheme 4. Diels–Alder reactions of cycloalkylidene derivatives **3a**, **5b** with cycloalkylenecycloalkane **12** and **14**.

Table 5

Energies of FMOs of heterodienes **3a**, **3b**, **3e**, **5a**, **5b**, **5e**, and dienophiles **6a**, **9**, **12**, **14** obtained by semi-empirical AM1, PM3, and ab initio HF/3-21G calculations

Compound	FMO	E/eV (AM1)	E/eV (PM3)	E/eV (HF)
3a	HOMO	−10.014	−10.119	−9.558
	LUMO	−0.304	−0.493	2.386
3b	HOMO	−10.064	−10.157	−9.574
	LUMO	−0.434	−0.616	2.152
3e	HOMO	−10.039	−10.150	−9.541
	LUMO	−0.405	−0.599	2.189
5a	HOMO	−10.439	−10.146	−10.386
	LUMO	−0.749	−0.909	1.932
5b	HOMO	−10.399	−10.082	−10.346
	LUMO	−0.786	−0.921	1.879
5e	HOMO	−10.429	−10.138	−10.345
	LUMO	−0.734	−0.897	1.939
6a	HOMO	−9.350	−9.459	−9.006
	LUMO	1.504	1.329	5.313
9	HOMO	−9.382	−9.498	−8.939
	LUMO	1.301	1.157	5.140
12	HOMO	−9.051	−9.222	−8.462
	LUMO	1.235	1.062	5.019
14	HOMO	−8.986	−9.068	−8.242
	LUMO	1.225	1.101	4.749

interaction of the LUMO orbital of heterodiene and the HOMO orbital of the dienophile (from 8.537 to 11.392 eV). For an inverse-electron-demand Diels–Alder cycloaddition the presence of an electron-withdrawing group in the heterodiene and an electron-releasing substituent in the dienophile contracts the LUMO(H)–HOMO(D) energy separation through raising the energy of the HOMO(D) and lowering the energy of the LUMO(H) and hence increases the reactivity.

This trend is observed in the present study too. Energy gaps $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$ for reaction of ethyl-vinyl ether **6a** are slightly lower for the cycloalkylidene derivatives of *N,N'*-dimethylbarbituric acid **5a**, **5b**, **5e**, than for the cycloalkylidene derivatives of benzoylacetone **3a**, **3b**, **3e** (Table 6). For the studied cycloadditions, the reactivity of cyclic enol ether **9** is comparable with the reactivity of ethyl-vinyl ether **6a**. The calculated energy gaps for the interaction LUMO orbital of heterodienes **3a**, **3e**, **5a**, **5e**, and HOMO orbital of dienophile **9** are similar to the appropriate energy gaps for heterodienes **3a**, **3e**, **5a**, **5e**, and dienophile **6a**. However, the frontier molecular orbital model does not seem capable of explaining the observed reactivity for cycloadditions of heterodienes **3a** or **5b** with cycloalkylenecycloalkanes **12** or **14**. The energy differences for the interaction of the LUMO orbital of **3a** or **5b** and the HOMO orbital of **12** or **14** are comparable or slightly lower than energy

Table 6

Energy gaps (eV): FMO interactions of heterodienes (H) **3a**, **3b**, **3e**, **5a**, **5b**, **5e** with dienophiles (D) **6a**, **9**, **12**, **14** obtained by semi-empirical AM1, PM3, and ab initio HF/3-21G calculations

Diels–Alder reaction	Method AM1 $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$	Method PM3 $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$	Method HF/3-21G $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$
3a (H) and 6a (D)	9.046	8.966	11.392
3b (H) and 6a (D)	8.916	8.842	11.158
3e (H) and 6a (D)	8.946	8.860	11.195
5a (H) and 6a (D)	8.602	8.550	10.938
5b (H) and 6a (D)	8.564	8.537	10.886
5e (H) and 6a (D)	8.617	8.562	10.945
3a (H) and 9 (D)	9.079	9.005	11.325
3e (H) and 9 (D)	8.978	8.899	11.128
5a (H) and 9 (D)	8.634	8.589	10.871
5e (H) and 9 (D)	8.649	8.601	10.878
3a (H) and 12 (D)	8.747	8.729	10.848
5b (H) and 14 (D)	8.200	8.147	10.122

gaps for reaction of **3a** or **5b** with dienophiles **6a** or **9** (Table 6). Probably, steric effects dictate that heterodienes **3a** and **5b** cannot react with sterically hindered dienophiles **12** or **14** and trispiropyrans **13** or **15** did not arise under these conditions.

3. Conclusion

In summary, Diels–Alder cycloadditions of sterically hindered cycloalkylidene derivatives of benzoylacetone and *N,N'*-dimethylbarbituric acid were studied. Potential heterodienes were synthesized in 77–87% yields by Knoevenagel condensation of benzoylacetone or *N,N'*-dimethylbarbituric acid with an appropriate cycloalkanone by heating at reflux in toluene or xylene in the presence of β -alanine and acetic acid as catalyst. The cycloaddition reactions of 2-cycloalkylidene-3-oxo-3-phenylpropionitriles or 5-cycloalkylidene-1,3-dimethylpyrimidine-2,4,6-triones with enol ethers, including cyclic enol ether 2-methylenetetrahydropyran, were performed in toluene solution at reflux and the spiroyrans and dispiropyrans were obtained in good 78–93% yields. To confirm the experimental results semi-empirical AM1, PM3 methods and ab initio Hartree–Fock calculations of frontier molecular orbital energies of heterodienes and dienophiles have been performed. Energy gaps $E_{\text{LUMO(H)}}-E_{\text{HOMO(D)}}$ for reaction of ethyl-vinyl ether are slightly lower for the cycloalkylidene derivatives of *N,N'*-dimethylbarbituric acid than for the cycloalkylidene derivatives of benzoylacetone. For the studied cycloadditions, the reactivity of cyclic enol ether is comparable with the reactivity of ethyl-vinyl ether.

4. Experimental

4.1. General

Melting points were determined on a Boetius hot stage apparatus. IR spectra: Bruker IFS 48 as films or in KBr pellets. NMR spectra: Bruker Avance II 300 (^1H : 300.18 MHz, ^{13}C : 75.48 MHz) in CDCl_3 with TMS as an internal standard. Mass spectra: Finnigan Mat 95 (70 eV). Microanalyses were performed with Euro EA 3000 Elemental Analyzer.

4.2. Materials

Benzoylacetone **1**, cycloalkanones **2a–e**, *N,N'*-dimethylbarbituric acid **4**, enol ethers **6a–c** were commercially available. 2-Cycloalkylidene-3-oxo-3-phenylpropionitriles **3a–e** and 5-cycloalkylidene-

1,3-dimethylpyrimidine-2,4,6-triones **5a–e** were obtained according to the procedure described in the literature.¹²

4.3. General procedure for Knoevenagel condensation

A mixture consisting of 10 mmol methylene compound **1** or **4**, 10 mmol cycloalkanone **2a–e**, β -alanine (180 mg, 2 mmol), acetic acid (2 mL), toluene or xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 4–6 h. The progress of the reactions was monitored by TLC. The solvent was evaporated and the mixture was purified by flash chromatography on silica gel using ethyl acetate/pet. ether 1:2 (**3a–e**) or ethyl acetate/pet. ether 1:1 (**5a–e**) as an eluent. Recrystallization from *n*-hexane (**3a, b**) or *n*-hexane/*tert*-butyl methyl ether 3:1 or 5:1 (**5a–e**) gave **3a–e** and **5a–e** with yields 77–87% listed in Table 1.

4.3.1. 2-Cycloheptylidene-3-oxo-3-phenylpropionitrile (3c). A mixture consisting of benzoylacetonitrile **1** (1.45 g, 10 mmol), cycloheptanone **2c** (1.12 g, 1.17 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in toluene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 5 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:2 EtOAc/pet. ether) to give the *title compound 3c* (2.01 g, 84%) as a colorless oil; [found: C, 80.35; H, 7.29; N, 5.82. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85%]; ν_{\max} (film) 3063, 2932, 2856, 2210, 1670, 1597 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.95–7.91 (2H, m, Ph), 7.65–7.59 (1H, m, Ph), 7.53–7.47 (2H, m, Ph), 2.89–2.85 (2H, m, cycloheptylidene), 2.61–2.57 (2H, m, cycloheptylidene), 1.88–1.81 (2H, m, cycloheptylidene), 1.74–1.52 (6H, m, cycloheptylidene); δ_C (75.5 MHz, $CDCl_3$) 189.3, 176.5, 136.0, 134.1, 129.5, 128.8, 116.3, 110.6, 36.9, 33.9, 29.1, 28.8, 26.7, 26.6; m/z (ESI) 240 (MH^+), 212, 158, 105.

4.3.2. 2-Cyclooctylidene-3-oxo-3-phenylpropionitrile (3d). A mixture consisting of benzoylacetonitrile **1** (1.45 g, 10 mmol), cyclooctanone **2d** (1.26 g, 1.32 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in toluene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 6 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:2 EtOAc/pet. ether) to give the *title compound 3d* (1.96 g, 82%) as a colorless oil; [found: C, 80.51; H, 7.63; N, 5.69. $C_{17}H_{19}NO$ requires C, 80.60; H, 7.56; N, 5.53%]; ν_{\max} (film) 3059, 2948, 2853, 2210, 1675, 1592 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.94–7.90 (2H, m, Ph), 7.64–7.58 (1H, m, Ph), 7.52–7.47 (2H, m, 2H, Ph), 2.78 (2H, ddd, J 3.6, 6.0, 8.7 Hz, cyclooctylidene), 2.58 (2H, ddd, J 3.9, 6.3, 9.0 Hz, cyclooctylidene), 2.03–1.95 (2H, m, cyclooctylidene), 1.80–1.77 (2H, m, cyclooctylidene), 1.62–1.47 (6H, m, cyclooctylidene); δ_C (75.5 MHz, $CDCl_3$) 189.2, 179.4, 136.1, 134.0, 129.4, 128.8, 116.6, 110.2, 35.7, 33.2, 27.4, 27.2, 26.5, 25.8, 25.6; m/z (ESI) 254 (MH^+), 105.

4.3.3. (3'R)-2-(3'-Methylcyclohexylidene)-3-oxo-3-phenylpropionitrile (3e). A mixture consisting of benzoylacetonitrile **1** (1.45 g, 10 mmol), (*R*)-(+)-3-methylcyclohexanone **2e** (1.12 g, 1.22 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in toluene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 6 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:2 EtOAc/pet. ether) to give the *title compound 3e* as a mixture of isomers *E/Z* (1:1) (1.94 g, 81%) as a colorless oil; [found: C, 80.37; H, 7.31; N, 5.89. $C_{16}H_{17}NO$ requires C, 80.30; H, 7.16; N, 5.85%]; ν_{\max} (film) 3063, 2932, 2856, 2210, 1670, 1597 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.96–7.92 (2H, m, Ph), 7.66–7.60 (1H, m, Ph), 7.53–7.48 (2H, m, Ph), 3.05–3.00 (1H, m, cyclohexylidene), 2.72–2.64 (1H, m, cyclohexylidene), 2.31 (1H, ddd, J 5.1, 12.6,

13.5 Hz, cyclohexylidene), 1.29–1.16, 2.11–1.80 (6H, m, cyclohexylidene), 0.91, 1.08 (3H, d, J 6.6 Hz, 3'-Me); δ_C (75.5 MHz, $CDCl_3$) 189.3, 189.2, 172.3, 172.1, 135.9, 134.2, 129.5, 128.9, 116.0, 108.3, 108.2, 43.4, 40.3, 35.2, 34.9, 33.9, 33.8, 32.1, 27.8, 27.1, 21.9; m/z (ESI) 240 (MH^+).

4.3.4. 5-Cyclohexylidene-1,3-dimethylpyrimidine-2,4,6-trione (5a). A mixture consisting of *N,N'*-dimethylbarbituric acid **4** (1.56 g, 10 mmol), cyclohexanone **2a** (0.98 g, 1.04 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 5 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:1 EtOAc/pet. ether). Recrystallization (3:1 *n*-hexane/*tert*-butyl methyl ether) gave the *title compound 5a* (1.94 g, 82%) as a white solid, mp 112 °C; [found: C, 61.13; H, 6.87; N, 12.01. $C_{12}H_{16}N_2O_3$ requires C, 61.00; H, 6.83; N, 11.86%]; ν_{\max} (KBr) 2936, 2833, 1741, 1702, 1658 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.33 (3H, s, N–Me), 3.32 (3H, s, N–Me), 3.08 (2H, t, J 6.6 Hz, cyclohexylidene), 2.10–1.56 (8H, m, cyclohexylidene); δ_C (75.5 MHz, $CDCl_3$) 184.2, 167.4, 162.5, 131.5, 129.5, 28.7, 28.5, 26.6, 25.6, 25.4, 22.4, 21.4; m/z (ESI) 237 (MH^+), 169, 157, 112, 83.

4.3.5. 5-Cyclopentylidene-1,3-dimethylpyrimidine-2,4,6-trione (5b). A mixture consisting of *N,N'*-dimethylbarbituric acid **4** (1.56 g, 10 mmol), cyclopentanone **2b** (0.84 g, 0.89 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 4 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:1 EtOAc/pet. ether). Recrystallization (3:1 *n*-hexane/*tert*-butyl methyl ether) gave the *title compound 5b* (1.93 g, 87%) as a white solid, mp 113 °C; [found: C, 59.46; H, 6.15; N, 12.67. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.35; N, 12.60%]; ν_{\max} (KBr) 2972, 2883, 1727, 1665, 1572 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.34 (6H, s, N–Me), 3.24 (4H, ddd, J 3.0, 7.5, 15.0 Hz, 2'-H), 1.81 (4H, m, 3'-H); δ_C (75.5 MHz, $CDCl_3$) 194.6, 161.8, 151.3, 135.3, 114.1, 39.6, 28.3, 25.8; m/z (ESI) 223 (MH^+), 213, 185, 169.

4.3.6. 5-Cycloheptylidene-1,3-dimethylpyrimidine-2,4,6-trione (5c). A mixture consisting of *N,N'*-dimethylbarbituric acid **4** (1.56 g, 10 mmol), cycloheptanone **2c** (1.12 g, 1.17 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 5 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:1 EtOAc/pet. ether). Recrystallization (5:1 *n*-hexane/*tert*-butyl methyl ether) gave the *title compound 5c* (2.15 g, 86%) as a white solid, mp 68 °C; [found: C, 62.22; H, 7.20; N, 11.18. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19%]; ν_{\max} (KBr) 2930, 2854, 1729, 1670, 1566 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.32 (6H, s, N–Me), 3.11 (4H, t, J 6.3 Hz, 2'-H), 1.90–1.82 (4H, m, cycloheptylidene), 1.57 (4H, m, cycloheptylidene); δ_C (75.5 MHz, $CDCl_3$) 187.7, 162.1, 151.3, 135.2, 117.9, 59.5, 38.3, 31.9, 28.7, 28.4, 27.8, 26.3, 26.1; m/z (ESI) 251 (MH^+), 169, 112, 83.

4.3.7. 5-Cyclooctylidene-1,3-dimethylpyrimidine-2,4,6-trione (5d). A mixture consisting of *N,N'*-dimethylbarbituric acid **4** (1.56 g, 10 mmol), cyclooctanone **2d** (1.26 g, 1.32 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 5 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:1 EtOAc/pet. ether). Recrystallization (5:1 *n*-hexane/*tert*-butyl methyl ether) gave the *title compound 5d* (2.15 g, 86%) as a white solid, mp 54 °C; [found: C, 63.58; H, 7.57; N, 10.74. $C_{14}H_{20}N_2O_3$ requires C, 63.62; H, 7.63; N, 10.60%]; ν_{\max} (KBr) 2933, 2854, 1724, 1667, 1526 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.15 (3H, s, N–Me), 3.14 (3H, s, N–Me), 2.11–2.07

(4H, m, cyclooctylidene), 1.92–1.84 (1H, m, cyclooctylidene), 1.44–1.39 (9H, m, cyclooctylidene); δ_C (75.5 MHz, $CDCl_3$) 187.2, 161.7, 151.6, 133.7, 131.9, 57.6, 36.0, 28.9, 28.1, 28.0, 27.5, 25.8, 25.2; m/z (ESI) 265 (MH^+).

4.3.8. (3'R)-(-)-5-(3'-Methylcyclohexylidene)-1,3-dimethylpyrimidine-2,4,6-trione (5e). A mixture consisting of *N,N'*-dimethylbarbituric acid **4** (1.56 g, 10 mmol), (R)-(+)-3-methylcyclohexanone **2e** (1.12 g, 1.22 mL, 10 mmol), β -alanine (180 mg, 2 mmol), glacial acetic acid (2 mL) in xylene (50 mL) was stirred and heated under reflux in a flask fitted with a Dean–Stark trap and condenser for 6 h. The solvent was evaporated and the mixture was purified by flash chromatography (1:1 EtOAc/pet. ether). Recrystallization (5:1 *n*-hexane/*tert*-butyl methyl ether) gave the *title compound* **5e** (1.93 g, 77%) as a white solid, mp 73 °C; [found: C, 62.51; H, 7.32; N, 11.26. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19%]; $[\alpha]_D^{25} -13.1$ (c 0.08, $CHCl_3$); $\nu_{max}(KBr)$ 2952, 2929, 2870, 1737, 1672, 1599 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 3.33 (3H, s, N–Me), 3.32 (3H, s, N–Me), 2.25–1.23 (9H, m, cyclohexylidene), 1.06 (3H, d, *J* 6.3 Hz, 3'-Me); δ_C (75.5 MHz, $CDCl_3$) 183.2, 167.3, 162.5, 130.9, 129.2, 57.7, 42.6, 37.0, 34.4, 34.2, 28.6, 28.5, 22.3; m/z (ESI) 251 (MH^+).

4.4. General procedure for the synthesis of spiropyrans **7a–g**, **8a–e**, and dispiropyrans **10a, b** and **11a, b**

A solution of 2-cycloalkylidene-3-oxo-3-phenylpropionitrile **3a–e** or 5-cycloalkylidene-1,3-dimethylpyrimidine-2,4,6-trione **5a–e** (5 mmol) in anhydrous toluene (10 mL), and 50 mmol the appropriate vinyl ethers **6a–c**, **9** (10 equiv) and some crystals of hydroquinone was heated at 110 °C in a pressure flask (a round-bottomed flask 100 mL with a screw cap and a Teflon seal) for the 24 h. The progress of the reactions was monitored by TLC. The solvent and excess of ethers were evaporated and the mixture was purified by column chromatography on silica gel using ethyl acetate/pet. ether 1:3 (**7a–f**), ethyl acetate/pet. ether 1:6 (**7g**), ethyl acetate/pet. ether 1:1 (**8a–d**), ethyl acetate/pet. ether 1:2 (**8e**, **10a, b**, **11a, b**) as an eluent. Recrystallization from *n*-hexane (**7a**, **7b**, **7e**, **7f**, **8a**, **8c**, **8e**) or *n*-hexane/*tert*-butyl methyl ether 5:1 (**7c**, **7d**, **10a**, **10b**, **11a**) gave **7a–g**, **8a–e**, **10a–b**, and **11a–b** with yields listed in Table 2.

4.4.1. (2'RS)-2'-Ethoxy-3',4'-dihydro-6'-phenylspiro[cyclohexane-1,4'-[2H]pyran]-5'-carbonitrile (7a). A solution of 2-cyclohexylidene-3-oxo-3-phenylpropionitrile **3a** (1.13 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the *title compound* **7a** (1.32 g, 89%) as a white solid, mp 115 °C; [found: C, 76.78; H, 7.84; N, 4.81. $C_{19}H_{23}NO_2$ requires C, 76.74; H, 7.80; N, 4.71%]; R_f (1:3 EtOAc/pet. ether) 0.47; $\nu_{max}(KBr)$ 2975, 2935, 2857, 2197, 1613, 1598, 1114, 1064 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.73–7.71 (2H, m, Ph), 7.42–7.40 (3H, m, Ph), 5.13 (1H, dd, *J* 2.4, 8.1 Hz, 2'-H), 4.06 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH_3), 3.70 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH_3), 2.26 (1H, dd, *J* 2.4, 13.8 Hz, 3'-H), 1.87–1.40 (11H, m, 3'-H, cyclohexane), 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (75.5 MHz, $CDCl_3$) 161.9, 133.5, 130.5, 128.3, 128.2, 119.3, 99.6, 95.8, 65.3, 36.9, 35.9, 35.4, 34.8, 25.1, 21.7, 21.2, 15.2; m/z (ESI) 298 (MH^+), 226, 153, 105.

4.4.2. (2'RS)-3',4'-Dihydro-2'-isobutoxy-6'-phenylspiro[cyclohexane-1,4'-[2H]pyran]-5'-carbonitrile (7b). A solution of 2-cyclohexylidene-3-oxo-3-phenylpropionitrile **3a** (1.13 g, 5 mmol) in anhydrous toluene (10 mL) and isobutyl-vinyl ether **6b** (5.02 g, 6.54 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of

ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the *title compound* **7b** (1.48 g, 91%) as a white solid, mp 47 °C; [found: C, 77.62; H, 8.63; N, 4.40. $C_{21}H_{27}NO_2$ requires C, 77.50; H, 8.36; N, 4.30%]; R_f (1:3 EtOAc/pet. ether) 0.49; $\nu_{max}(KBr)$ 2973, 2933, 2855, 2204, 1607, 1574, 1147, 1051 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.73–7.70 (2H, m, Ph), 7.43–7.40 (3H, m, Ph), 5.13 (1H, dd, *J* 2.7, 7.2 Hz, 2'-H), 3.76 (1H, dd, *J* 6.6, 9.0 Hz, $OCH_2CH(CH_3)_2$), 3.38 (1H, dd, *J* 6.6, 9.0 Hz, $OCH_2CH(CH_3)_2$), 2.17 (1H, dd, *J* 2.7, 13.8 Hz, 3'-H), 1.92–0.88 (12H, m, $OCH_2CH(CH_3)_2$, 3-H, cyclohexane), 0.95 (6H, d, *J* 6.9 Hz, $OCH_2CH(CH_3)_2$); δ_C (75.5 MHz, $CDCl_3$) 161.9, 133.6, 130.5, 128.3, 128.2, 119.3, 99.8, 95.8, 76.4, 36.6, 36.4, 35.0, 34.4, 28.6, 25.2, 21.6, 21.3, 19.4, 19.3; m/z (ESI) 326(MH^+), 226, 181, 105.

4.4.3. (2'RS)-3',4'-Dihydro-2'-methoxy-2'-methyl-6'-phenylspiro[cyclohexane-1,4'-[2H]pyran]-5'-carbonitrile (7c). A solution of 2-cyclohexylidene-3-oxo-3-phenylpropionitrile **3a** (1.13 g, 5 mmol) in anhydrous toluene (10 mL) and isopropenyl-methyl ether **6c** (3.62 g, 4.72 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether). Recrystallization (*n*-hexane/*tert*-butyl methyl ether 5:1) gave the *title compound* **7c** (1.25 g, 84%) as a white solid, mp 122 °C; [found: C, 76.50; H, 7.63; N, 4.80. $C_{19}H_{23}NO_2$ requires C, 76.74; H, 7.80; N, 4.71%]; R_f (1:3 EtOAc/pet. ether) 0.51; $\nu_{max}(KBr)$ 2975, 2927, 2856, 2199, 1612, 1575, 1100, 1063 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.75–7.72 (2H, m, Ph), 7.42–7.40 (3H, m, Ph), 3.35 (3H, s, OMe), 2.56 (1H, d, *J* 14.4 Hz, 3'-H), 2.22–2.19 (1H, m, 3'-H), 1.57 (3H, s, 2'-Me), 1.91–1.22 (10H, m, cyclohexane); δ_C (75.5 MHz, $CDCl_3$) 160.8, 134.0, 130.3, 128.3, 119.6, 101.3, 96.9, 49.5, 39.8, 38.9, 34.4, 32.6, 25.4, 23.4, 22.1, 21.0; m/z (ESI) 320 (MNa^+), 298(MH^+), 280, 266, 238, 226, 105.

4.4.4. (2'RS)-2'-Ethoxy-3',4'-dihydro-6'-phenylspiro[cyclopentane-1,4'-[2H]pyran]-5'-carbonitrile (7d). A solution of 2-cyclopentylidene-3-oxo-3-phenylpropionitrile **3b** (1.06 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone were heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether). Recrystallization (*n*-hexane/*tert*-butyl methyl ether 5:1) gave the *title compound* **7d** (1.23 g, 87%) as a white solid, mp 72 °C; [found: C, 76.41; H, 7.53; N, 4.82. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%]; R_f (1:3 EtOAc/pet. ether) 0.57; $\nu_{max}(KBr)$ 2969, 2947, 2871, 2200, 1613, 1599, 1114, 1061 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.74–7.71 (2H, m, Ph), 7.44–7.40 (3H, m, Ph), 5.14 (1H, dd, *J* 2.4, 7.8 Hz, 2'-H), 4.06 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH_3), 3.70 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH_3), 1.98 (1H, dd, *J* 2.4, 13.8 Hz, 3'-H), 1.85–1.57 (9H, m, 3-H, cyclopentane), 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (75.5 MHz, $CDCl_3$) 161.8, 133.5, 130.5, 128.3, 128.2, 119.4, 100.1, 93.7, 65.2, 42.5, 40.2, 38.9, 24.5, 24.0, 15.2; m/z (ESI) 306 (MNa^+), 284 (MH^+), 212, 139, 105.

4.4.5. (2'RS)-2'-Ethoxy-3',4'-dihydro-6'-phenylspiro[cycloheptane-1,4'-[2H]pyran]-5'-carbonitrile (7e). A solution of 2-cycloheptylidene-3-oxo-3-phenylpropionitrile **3c** (1.20 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone were heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the *title compound* **7e** (1.34 g, 86%) as a white solid, mp 105 °C; [found: C, 77.00; H, 8.02; N, 4.62. $C_{20}H_{25}NO_2$ requires C, 77.14; H, 8.09; N, 4.50%]; R_f (1:3 EtOAc/pet. ether) 0.54; $\nu_{max}(KBr)$ 2979, 2943, 2925, 2854, 2200, 1610, 1597, 1159, 1071 cm^{-1} ; δ_H (300 MHz, $CDCl_3$) 7.72–7.68 (2H, m, Ph), 7.44–7.37 (3H, m, Ph), 5.17

(1H, dd, *J* 2.4, 8.1 Hz, 2'-H), 4.06 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.70 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 2.10 (1H, dd, *J* 2.4, 13.8 Hz, 3'-H), 2.03–1.54 (13H, m, 3'-H, cycloheptane), 1.29 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 161.1, 133.5, 130.4, 128.3, 128.2, 119.9, 99.5, 96.0, 65.2, 40.8, 40.2, 38.4, 37.9, 29.5, 29.3, 23.0, 22.9, 15.2; *m/z* (ESI) 334 (MNa⁺), 312(MH⁺), 240, 167, 158, 105.

4.4.6. (2'RS)-2'-Ethoxy-3',4'-dihydro-6'-phenylspiro[cyclooctane-1,4'-[2H]pyran]-5'-carbonitrile (7f). A solution of 2-cyclooctylidene-3-oxo-3-phenylpropionitrile **3d** (1.27 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:3 EtOAc/pet. ether) to give the title compound **7f** (1.35 g, 83%) as a colorless oil; [found: C, 77.72; H, 8.51; N, 4.53. C₂₁H₂₇NO₂ requires C, 77.50; H, 8.36; N, 4.30%]; *R_f* (1:3 EtOAc/pet. ether) 0.55; ν_{max} (film) 2985, 2943, 2931, 2853, 2215, 1610, 1592, 1153, 1068 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 7.95–7.90 (2H, m, Ph), 7.69–7.59 (1H, m, Ph), 7.53–7.48 (2H, m, Ph), 5.22 (1H, dd, *J* 2.7, 8.4 Hz, 2'-H), 4.04 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.68 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 2.08 (1H, dd, *J* 2.7, 13.5 Hz, 3'-H), 2.03–1.47 (15H, m, 3'-H, cyclooctane), 1.26 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 161.5, 136.1, 134.0, 129.4, 128.6, 116.6, 110.2, 99.4, 65.2, 39.1, 36.9, 35.7, 33.2, 27.4, 27.2, 26.5, 25.8, 25.6, 15.2; *m/z* (ESI) 348 (MNa⁺), 326(MH⁺), 158, 105.

4.4.7. Diastereoisomer A (–)-2'-Ethoxy-3',4'-dihydro-3-methyl-6'-phenylspiro[cyclohexane-1,4'-[2H]pyran]-5'-carbonitrile (7g). A solution of (3'R)-2-(3'-methylcyclohexylidene)-3-oxo-3-phenylpropionitrile **3e** (1.20 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:6 EtOAc/pet. ether) to give the title compound **7g** (0.94 g, 61%) as a colorless oil; [found: C, 77.31; H, 8.20; N, 4.48. C₂₀H₂₅NO₂ requires C, 77.14; H, 8.09; N, 4.50%]; *R_f* (1:6 EtOAc/pet. ether) 0.48; ν_{max} (film) 2952, 2928, 2870, 2200, 1593, 1572, 1156, 1072 cm⁻¹; [α]_D²² –34.2 (c 0.12, CHCl₃); δ_{H} (300 MHz, CDCl₃) 7.69–7.66 (2H, m, Ph), 7.43–7.40 (3H, m, Ph), 5.28 (1H, dd, *J* 3.0, 8.4 Hz, 2'-H), 4.03 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.68 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 1.11–1.03, 1.45–1.35, 2.32–1.60 (11H, m, 3'-H, cyclohexane), 1.27 (3H, t, *J* 7.2 Hz, OCH₂CH₃), 0.91 (3H, d, *J* 6.6 Hz, 3-Me); δ_{C} (75.5 MHz, CDCl₃) 162.8, 133.9, 128.5, 127.5, 127.2, 120.5, 99.3, 91.6, 64.1, 45.6, 42.4, 37.9, 34.0, 32.6, 26.3, 21.6, 20.0, 14.1; *m/z* (ESI) 312(MH⁺).

Diastereoisomer **A** of the compound **7g** (0.6 g, 2 mmol) was submitted to the action of boron trifluoride diethyl etherate BF₃Et₂O (5 mL) and a mixture of diastereoisomer **A** and a new diastereoisomer **B** (**A/B**=1:2.3) was obtained after 24 h at room temperature. The diastereoisomers **A** and **B** were separated by column chromatography (1:6 EtOAc/pet. ether). The diastereoisomer **B** of compound **7g** (0.37 g) was obtained as a colorless oil; [found: C, 77.29; H, 8.15; N, 4.57. C₂₀H₂₅NO₂ requires C, 77.14; H, 8.09; N, 4.50%]; *R_f* (1:6 EtOAc/pet. ether) 0.54; ν_{max} (film) 2975, 2935, 2857, 2197, 1613, 1598, 1114, 1064 cm⁻¹; [α]_D²² –27.2 (c 0.12, CHCl₃); δ_{H} (300 MHz, CDCl₃) 7.71–7.66 (2H, m, Ph), 7.42–7.39 (3H, m, Ph), 5.34 (1H, dd, *J* 5.4, 6.0 Hz, 2'-H), 4.03 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.68 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 2.30–1.57, 1.45–1.35, 1.14–1.03 (11H, m, 3'-H, cyclohexane), 1.29 (3H, t, *J* 7.2 Hz, OCH₂CH₃), 0.89 (3H, d, *J* 6.6 Hz, 3-Me); δ_{C} (75.5 MHz, CDCl₃) 163.0, 132.7, 129.3, 127.6, 127.1, 120.6, 98.2, 91.2, 64.1, 47.0, 42.8, 35.9, 33.7, 32.9, 26.6, 21.9, 20.3, 14.1; *m/z* (ESI) 312(MH⁺).

4.4.8. (7'RS)-7'-Ethoxy-1',5',6',7'-tetrahydro-1',3'-dimethylspiro[cyclohexane-1,5'-[2H]pyrano[2,3-d]pyrimidine]-2',4'(3'H)-dione

(**8a**). A solution of 5-cyclohexylidene-1,3-dimethylpyrimidine-2,4,6-trione **5a** (1.18 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:1 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the title compound **8a** (1.22 g, 79%) as a white solid, mp 75 °C; [found: C, 62.44; H, 7.89; N, 9.32. C₁₆H₂₄N₂O₄ requires C, 62.32; H, 7.84; N, 9.08%]; *R_f* (1:1 EtOAc/pet. ether) 0.49; ν_{max} (KBr) 2977, 2925, 2863, 1707, 1638, 1614, 1161 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 5.13 (1H, dd, *J* 2.1, 8.4 Hz, 7'-H), 3.99 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.69 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.36 (3H, s, N-Me), 3.31 (3H, s, N-Me), 2.75 (1H, ddd, *J* 4.2, 8.7, 12.9 Hz, cyclohexane), 2.51 (1H, ddd, *J* 4.2, 9.3, 12.9 Hz, cyclohexane), 2.36 (1H, dd, *J* 2.1, 14.1 Hz, 6'-H), 1.71 (1H, ddd, *J* 1.2, 8.4, 14.1 Hz, 6'-H), 1.63–1.26 (8H, m, cyclohexane), 1.31 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 161.9, 154.1, 150.9, 101.2, 95.2, 65.7, 36.4, 28.7, 27.7, 34.5, 33.9, 33.1, 25.1, 21.9, 21.6, 15.1; *m/z* (ESI) 309(MH⁺), 263, 237, 213, 185, 169, 112.

4.4.9. (7'RS)-7'-Ethoxy-1',5',6',7'-tetrahydro-1',3'-dimethylspiro[cyclopentane-1,5'-[2H]pyrano[2,3-d]pyrimidine]-2',4'(3'H)-dione (8b). A solution of 5-cyclopentylidene-1,3-dimethylpyrimidine-2,4,6-trione **5d** (1.11 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:1 EtOAc/pet. ether) to give the title compound **8b** (1.37 g, 93%) as a colorless oil; [found: C, 61.29; H, 7.62; N, 9.47. C₁₅H₂₂N₂O₄ requires C, 61.21; H, 7.53; N, 9.52%]; *R_f* (1:1 EtOAc/pet. ether) 0.45; ν_{max} (film) 2955, 2873, 1704, 1645, 1613, 1178 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 5.08 (1H, dd, *J* 2.1, 8.1 Hz, 7'-H), 3.93 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.65 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.30 (3H, s, N-Me), 3.25 (3H, s, N-Me), 2.37 (1H, ddd, *J* 3.0, 6.9, 12.6 Hz, cyclopentane), 2.16 (1H, ddd, *J* 3.9, 8.7, 12.6 Hz, cyclopentane), 1.93 (1H, dd, *J* 2.1, 13.8 Hz, 6'-H), 1.72 (1H, dd, *J* 8.1, 13.8 Hz, 6'-H), 1.87–1.38 (6H, m, cyclopentane), 1.24 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 161.7, 153.7, 150.8, 101.8, 93.7, 65.6, 41.7, 40.3, 38.8, 36.9, 28.6, 27.6, 25.5, 25.1, 14.9; *m/z* (ESI) 295(MH⁺), 221.

4.4.10. (7'RS)-7'-Ethoxy-1',5',6',7'-tetrahydro-1',3'-dimethylspiro[cycloheptane-1,5'-[2H]pyrano[2,3-d]pyrimidine]-2',4'(3'H)-dione (8c). A solution of 5-cycloheptylidene-1,3-dimethylpyrimidine-2,4,6-trione **5c** (1.25 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:1 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the title compound **8c** (1.47 g, 91%) as a white solid, mp 100 °C; [found: C, 63.62; H, 8.33; N, 8.52. C₁₇H₂₆N₂O₄ requires C, 63.33; H, 8.13; N, 8.69%]; *R_f* (1:1 EtOAc/pet. ether) 0.47; ν_{max} (KBr) 2972, 2928, 2878, 2858, 1705, 1639, 1621, 1156 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 5.18 (1H, dd, *J* 2.1, 8.7 Hz, 7'-H), 4.00 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.71 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.35 (3H, s, N-Me), 3.31 (3H, s, N-Me), 2.74 (1H, ddd, *J* 2.4, 8.7, 11.1 Hz, cycloheptane), 2.42 (1H, ddd, *J* 1.8, 9.3, 11.1 Hz, cycloheptane), 2.23 (1H, dd, *J* 2.4, 13.8 Hz, 6'-H), 1.75 (1H, dd, *J* 8.7, 13.8 Hz, 6'-H), 1.68–1.36 (10H, m, cycloheptane), 1.31 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 162.1, 153.2, 150.9, 101.2, 97.4, 65.8, 39.4, 39.3, 37.8, 37.4, 28.8, 28.5, 28.2, 27.8, 23.8, 23.1, 15.1; *m/z* (ESI) 323(MH⁺), 277, 251, 213, 185, 169, 112.

4.4.11. (7'RS)-7'-Ethoxy-1',5',6',7'-tetrahydro-1',3'-dimethylspiro[cyclooctane-1,5'-[2H]pyrano[2,3-d]pyrimidine]-2',4'(3'H)-dione (8d). A solution of 5-cyclooctylidene-1,3-dimethylpyrimidine-2,4,6-

trione **5d** (1.32 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:1 EtOAc/pet. ether). Recrystallization (*n*-hexane) gave the *title compound* **8d** (1.48 g, 88%) as a white solid, mp 138 °C; [found: C, 64.28; H, 8.47; N, 8.45. C₁₈H₂₈N₂O₄ requires C, 64.26; H, 8.39; N, 8.33%]; *R*_f (1:1 EtOAc/pet. ether) 0.63; ν_{\max} (KBr) 2972, 2928, 2878, 2858, 1705, 1639, 1621, 1156 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 5.20 (1H, dd, *J* 2.4, 8.7 Hz, 7'-H), 4.00 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.70 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.36 (3H, s, N-Me), 3.32 (3H, s, N-Me), 2.92 (1H, ddd, *J* 2.4, 8.1, 14.7 Hz, 6'-H), 2.45 (1H, dd, *J* 8.1, 14.7 Hz, 6'-H), 2.27 (1H, dd, *J* 2.4, 14.1 Hz, cyclooctane), 1.99–1.87 (1H, m, cyclooctane), 1.74–1.35 (12H, m, cyclooctane), 1.31 (3H, t, *J* 7.2 Hz, OCH₂CH₃); δ_{C} (75.5 MHz, CDCl₃) 162.3, 153.6, 150.9, 101.1, 97.3, 65.8, 36.9, 39.1, 35.4, 34.5, 28.8, 28.5, 28.4, 27.9, 23.1, 22.0, 21.9, 15.1; *m/z* (ESI) 337(MH⁺).

4.4.12. Diastereoisomer A (–)-7'-Ethoxy-1',5',6',7'-tetrahydro-1',3',3'-trimethylspiro[cyclohexane-1,5'-[2H]pyrano[2,3-d]pyrimidine]-2',4'-(3'H)-dione (**8e**). A solution of (3'R)-(–)-5-(3'-methylcyclohexylidene)-1,3-dimethylpyrimidine-2,4,6-trione **5e** (1.25 g, 5 mmol) in anhydrous toluene (10 mL) and ethyl-vinyl ether **6a** (3.62 g, 4.80 mL, 50 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent and excess of ether were evaporated and the mixture was purified by column chromatography (1:2 EtOAc/pet. ether) to give the *title compound* **8e** (1.26 g, 78%) as a colorless oil; [found: C, 63.41; H, 8.27; N, 8.82. C₁₇H₂₆N₂O₄ requires C, 63.33; H, 8.13; N, 8.69%]; *R*_f (1:2 EtOAc/pet. ether) 0.36; $[\alpha]_{\text{D}}^{22}$ –42.3 (c 0.21, CHCl₃); ν_{\max} (film) 2967, 2909, 2868, 2850, 1706, 1648, 1157 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 4.99 (1H, dd, *J* 2.4, 8.7 Hz, 7'-H), 3.92 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.63 (1H, dq, *J* 7.2, 9.3 Hz, OCH₂CH₃), 3.28 (3H, s, N-Me), 3.23 (3H, s, N-Me), 2.75 (1H, dd, *J* 6.0, 13.5 Hz, 2-H), 2.39 (1H, m, 3-H), 2.29 (1H, dd, *J* 2.4, 13.8 Hz, 6'-H), 2.09 (1H, m, 2-H), 1.69 (1H, ddd, *J* 1.2, 9.0, 14.1 Hz, 6'-H), 1.64–1.51 (3H, m, cyclohexane), 1.23–1.16 (3H, m, cyclohexane), 1.25 (3H, t, *J* 7.2 Hz, OCH₂CH₃), 0.97 (3H, d, *J* 7.2 Hz, 3-Me); δ_{C} (75.5 MHz, CDCl₃) 161.9, 154.3, 150.8, 101.0, 95.6, 65.8, 40.6, 40.0, 34.7, 33.1, 30.3, 28.7, 27.8, 27.7, 21.3, 17.0, 15.1; *m/z* (ESI) 323(MH⁺).

Diastereoisomer **A** of the compound **8e** (0.7 g, 2 mmol) was submitted to the action of boron trifluoride diethyl etherate BF₃Et₂O (5 mL) and a mixture of diastereoisomer **A** and a new diastereoisomer **B** (**A/B**=1:1.9) was obtained after 24 h at room temperature. The diastereoisomers **A** and **B** were separated by column chromatography (1:6 EtOAc/pet. ether). The diastereoisomer **B** of compound **8e** (0.39 g) was obtained as a colorless oil; [found: C, 63.25; H, 8.22; N, 8.74. C₁₇H₂₆N₂O₄ requires C, 63.33; H, 8.13; N, 8.69%]; *R*_f (1:2 EtOAc/pet. ether) 0.43; $[\alpha]_{\text{D}}^{22}$ –31.5 (c 0.21, CHCl₃); ν_{\max} (film) 2969, 2912, 2863, 2848, 1701, 1644, 1149 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 5.23 (1H, dd, *J* 2.4, 7.5 Hz, 7'-H), 3.97 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.69 (1H, dq, *J* 7.2, 9.6 Hz, OCH₂CH₃), 3.36 (3H, s, N-Me), 3.31 (3H, s, N-Me), 2.68 (1H, m, 3-H), 2.48 (1H, dd, *J* 6.0, 13.8 Hz, 2-H), 2.24 (1H, dd, *J* 2.4, 14.1 Hz, 6'-H), 2.09 (1H, m, 2-H), 1.87 (1H, dd, *J* 7.5, 14.1 Hz, 6'-H), 1.69–1.59 (3H, m, cyclohexane), 1.34–1.26 (3H, m, cyclohexane), 1.30 (3H, t, *J* 7.2 Hz, OCH₂CH₃), 1.03 (3H, d, *J* 7.2 Hz, 3-Me); δ_{C} (75.5 MHz, CDCl₃) 161.9, 154.1, 150.9, 101.0, 95.8, 65.6, 41.6, 41.2, 34.2, 32.6, 30.1, 28.8, 27.8, 27.3, 22.1, 17.6, 15.1; *m/z* (ESI) 323(MH⁺).

4.4.13. (2'RS)-3',4',3'',4'',5'',6''-hexahydro-6'-phenyldispiro[cyclohexane-1,4'-[2H]pyran-2',2''-[2H]pyran]-5'-carbonitrile (10a). A solution of 2-cyclohexylidene-3-oxo-3-phenylpropionitrile **3a** (1.13 g, 5 mmol) in anhydrous toluene (10 mL) and 2-methylenetetrahydropyran **9** (0.49 g, 5 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent

was evaporated and the mixture was purified by column chromatography (1:2 EtOAc/pet. ether). Recrystallization (*n*-hexane/*tert*-butyl methyl ether 5:1) gave the *title compound* **10a** (1.50 g, 93%) as a white solid, mp 134 °C; [found: C, 78.08; H, 7.84; N, 4.51. C₂₁H₂₅N₂O₂ requires C, 77.99; H, 7.79; N, 4.33%]; *R*_f (1:2 EtOAc/pet. ether) 0.61; ν_{\max} (KBr) 2956, 2930, 2857, 2197, 1620, 1161 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 7.80–7.77 (2H, m, Ph), 7.43–7.41 (3H, m, Ph), 3.84 (1H, ddd, *J* 3.9, 5.1, 11.4 Hz, 6'-H), 3.71 (1H, ddd, *J* 1.8, 4.0, 10.8 Hz, 6'-H), 2.44 (1H, d, *J* 14.4 Hz, 3'-H), 2.21–2.16 (1H, br, 3'-H), 2.01–1.22 (16H, m, cyclohexane, and tetrahydropyran); δ_{C} (75.5 MHz, CDCl₃) 160.6, 134.2, 130.2, 128.3, 128.2, 119.7, 99.0, 96.6, 62.2, 39.7, 39.0, 34.9, 34.2, 32.8, 25.3, 24.6, 22.0, 21.0, 18.4; *m/z* (ESI) 324(MH⁺).

4.4.14. (–)-3',4',3'',4'',5'',6''-Hexahydro-3-methyl-6'-phenyldispiro[cyclohexane-1,4'-[2H]pyran-2',2''-[2H]pyran]-5'-carbonitrile (10b). A solution of (3'R)-2-(3'-methylcyclohexylidene)-3-oxo-3-phenylpropionitrile **3e** (1.20 g, 5 mmol) in anhydrous toluene (10 mL) and 2-methylenetetrahydropyran **9** (0.49 g, 5 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent was evaporated and the mixture was purified by column chromatography (1:2 EtOAc/pet. ether). Recrystallization (*n*-hexane/*tert*-butyl methyl ether 5:1) gave the *title compound* **10b** (1.54 g, 91%) as a white solid, mp 185 °C; [found: C, 78.44; H, 8.25; N, 4.40. C₂₂H₂₇N₂O₂ requires C, 78.30; H, 8.06; N, 4.15%]; *R*_f (1:2 EtOAc/pet. ether) 0.51; $[\alpha]_{\text{D}}^{22}$ –74.5 (c 0.13, CHCl₃); ν_{\max} (KBr) 2949, 2915, 2869, 2195, 1588, 1152 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 7.72–7.69 (2H, m, Ph), 7.43–7.41 (3H, m, Ph), 0.89 (3H, d, *J* 6.3 Hz, 3-CH₃), 3.89 (1H, ddd, *J* 3.6, 4.8, 11.4 Hz, 6'-H), 3.77 (1H, ddd, *J* 1.8, 4.3, 11.0 Hz, 6'-H), 2.45 (1H, ddd, *J* 1.8, 1.8, 13.8 Hz, 3'-H), 2.34–2.27 (1H, m, cyclohexane, and tetrahydropyran), 2.21–2.12 (1H, m, 3'-H), 1.99–1.57 (12H, m, cyclohexane, and tetrahydropyran), 1.99–1.07 (1H, m, cyclohexane, and tetrahydropyran), 1.45–1.34 (1H, m, cyclohexane, and tetrahydropyran); δ_{C} (75.5 MHz, CDCl₃) 162.7, 134.5, 130.1, 128.7, 128.2, 122.4, 99.4, 93.1, 62.2, 49.1, 47.5, 38.5, 35.0, 34.0, 33.9, 27.6, 24.5, 23.0, 21.6, 18.3; *m/z* (ESI) 338(MH⁺).

4.4.15. (7'RS)-1',5',6',7',3'',4'',5'',6''-Oktahydro-1',3'-dimethyldispiro[cyclohexane-1,5'-[2H]pyrano[2,3-d]pyrimidine-7',2''-[2H]pyran]-2',4'(3'H)-dione (11a). A solution of 5-cyclohexylidene-1,3-dimethylpyrimidine-2,4,6-trione **5a** (1.18 g, 5 mmol) in anhydrous toluene (10 mL) and 2-methylenetetrahydropyran **9** (0.49 g, 5 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent was evaporated and the mixture was purified by column chromatography (1:2 EtOAc/pet. ether). Recrystallization (*n*-hexane/*tert*-butyl methyl ether 5:1) gave the *title compound* **11a** (1.45 g, 87%) as a white solid, mp 162 °C; [found: C, 64.81; H, 7.89; N, 8.54. C₁₈H₂₆N₂O₄ requires C, 64.65; H, 7.84; N, 8.38%]; *R*_f (1:2 EtOAc/pet. ether) 0.55; ν_{\max} (KBr) 2974, 2937, 2872, 1703, 1644, 1623, 1168, 1048 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 3.72 (1H, ddd, *J* 1.8, 3.9, 10.8 Hz, 6'-H), 3.59 (1H, ddd, *J* 3.9, 4.5, 11.7 Hz, 6'-H), 3.42 (3H, s, N-CH₃), 3.32 (3H, s, N-CH₃), 2.77 (1H, m, cyclohexane or tetrahydropyran), 2.54 (1H, d, *J* 14.4 Hz, 6'-H), 2.32 (1H, d, *J* 13.9 Hz, 6'-H), 1.91–1.04 (15H, m, cyclohexane, and tetrahydropyran); δ_{C} (75.5 MHz, CDCl₃) 162.1, 153.5, 151.1, 101.4, 95.4, 62.4, 40.5, 36.3, 34.6, 33.7, 30.2, 28.6, 27.7, 25.4, 24.3, 22.2, 21.6, 18.6; *m/z* (ESI) 335(MH⁺).

4.4.16. (–)-1',5',6',7',3'',4'',5'',6''-Oktahydro-1',3'-trimethyldispiro[cyclohexane-1,5'-[2H]pyrano[2,3-d]pyrimidine-7',2''-[2H]pyran]-2',4'(3'H)-dione (11b). A solution of (3'R)-(–)-5-(3'-methylcyclohexylidene)-1,3-dimethylpyrimidine-2,4,6-trione **5e** (1.25 g, 5 mmol) in anhydrous toluene (10 mL) and 2-methylenetetrahydropyran **9** (0.49 g, 5 mmol) and some crystals of hydroquinone was heated at 110 °C in a pressure flask for the 24 h. The solvent was

evaporated and the mixture was purified by column chromatography (1:2 EtOAc/pet. ether) to give the *title compound* **11b** (1.55 g, 89%) as a colorless oil; [found: C, 65.72; H, 8.19; N, 8.15. C₁₉H₂₈N₂O₄ requires C, 65.49; H, 8.10; N, 8.04%]; *R*_f (1:2 EtOAc/pet. ether) 0.41; [α]_D²⁵ –63.2 (c 0.15, CHCl₃); ν_{max} (film) 2946, 2915, 2870, 1701, 1638, 1623, 1167, 1047 cm^{–1}; δ_{H} (300 MHz, CDCl₃) 3.64 (1H, ddd, *J* 2.0, 4.1, 11.2 Hz, 6'-H), 3.54 (1H, ddd, *J* 3.9, 4.2, 11.5 Hz, 6'-H), 3.35 (3H, s, N–Me), 3.24 (3H, s, N–Me), 2.78 (1H, m, cyclohexane, and tetrahydropyran), 2.63 (1H, d, *J* 13.8 Hz, 6'-H), 2.41 (1H, d, *J* 14.0 Hz, 6'-H), 1.97–1.18 (15H, m, cyclohexane, and tetrahydropyran), 0.96 (3H, d, *J* 7.2 Hz, 3-Me); δ_{C} (75.5 MHz, CDCl₃) 162.0, 153.5, 151.0, 100.8, 95.2, 62.4, 41.6, 35.7, 34.5, 34.1, 30.8, 28.7, 27.7, 25.0, 24.2, 22.7, 21.3, 18.5, 17.6; *m/z* (ESI) 349(MH⁺).

Frontier orbital (HOMO and LUMO) energies of heterodienes **3a**, **3b**, **3e**, **5a**, **5b**, **5e** and dienophiles **6a**, **9**, **12**, **14** were calculated by semi-empirical AM1 and PM3 methods and ab initio Hartree–Fock calculations using the Gaussian 03 suite of programs. The geometries were fully optimized by PM3 semi-empirical methods and used as the basis for optimization at the Hartree–Fock level using the 3-21G basis set (HF/3-21G).

Acknowledgements

We thank the ACK Cyfronet for generous allocation of computing time on SGI Altix 3700 (Gaussian 03 suite of programs, grant No. MNiSW/SGI3700/UJ/084/2009).

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