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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

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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 dispirouracils 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.

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, antihypertensive, 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 policyclic 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 acid[9] 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

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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]

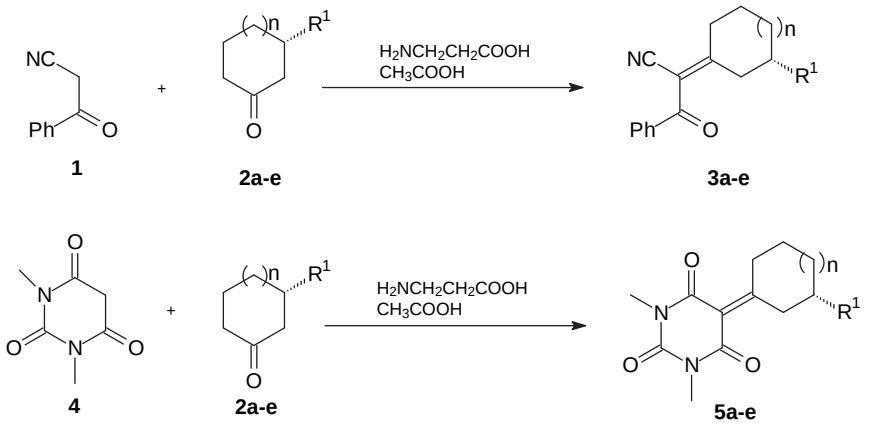
2. Results and discussion

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).

Compounds **7a**–**g** and **8a**–**e** were characterized by ^{1}H, ^{13}C NMR, IR, mass spectra, and elemental analysis. The ^{1}H and ^{13}C 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 ^{1}H 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 conformation[13] (Table 3).

In the ^{1}H 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 ^{1}H 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,



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	*n*	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

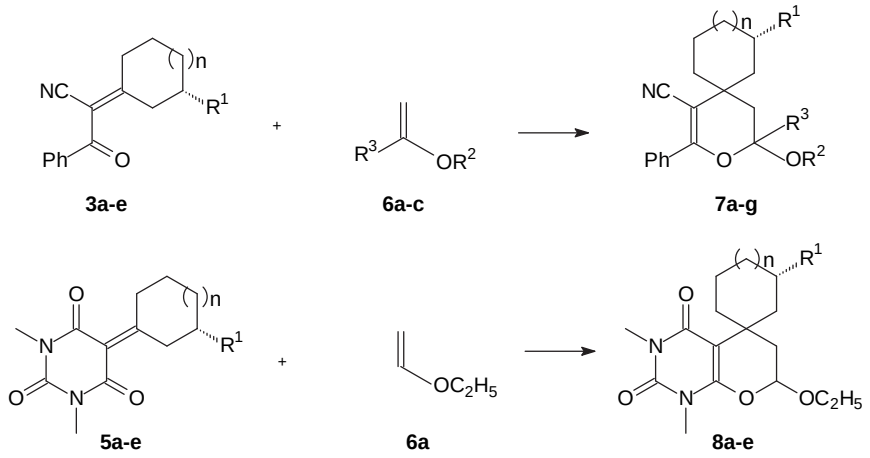
[a] Reaction mixture was heated to reflux in toluene (t) or xylene (x).

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.

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 BF_3Et_2O. 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 ^{1}H 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-methylenetetrahydropyrane **9**. The compound **9** was prepared according to the literature with a yield of 69% from 2-(chloromethyl)tetrahydropyrane[14] 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 spiropyrans **7a**–**g** and **8a**–**e** by Diels–Alder reactions

Diene	*n*	R^1	Enol ether	R^2	R^3	Spiropyran	Yield %[a]
3a	1	H	**6a**	C_2H_5	H	**7a**	89
3a	1	H	**6b**	*i*-Bu	H	**7b**	91
3a	1	H	**6c**	CH_3	CH_3	**7c**	84
3b	0	H	**6a**	C_2H_5	H	**7d**	87
3c	2	H	**6a**	C_2H_5	H	**7e**	86
3d	3	H	**6a**	C_2H_5	H	**7f**	83
3e	1	CH_3	**6a**	C_2H_5	H	**7g**	87
5a	1	H	**6a**	C_2H_5	H	**8a**	79
5b	0	H	**6a**	C_2H_5	H	**8b**	93
5c	2	H	**6a**	C_2H_5	H	**8c**	91
5d	3	H	**6a**	C_2H_5	H	**8d**	88
5e	1	CH_3	**6a**	C_2H_5	H	**8e**	78

[a] Isolated yields after column chromatography.

Table 3
Signals of protons 2′-H and 7′-H in ^{1}H 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		

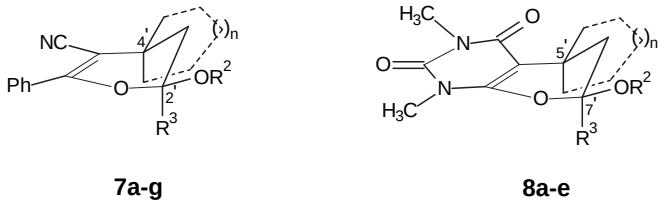


Fig. 1. Preferred configurations and conformations of spirocycloadducts **7a**–**g** and **8a**–**e** based on ^{1}H NMR analysis.

and **5e** with **9** were performed in toluene solution at 110 °C for 24 h and the spiropyrans **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 ^{1}H, ^{13}C NMR, IR, mass spectra, and elemental analysis. ^{1}H and ^{13}C 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 dispiropyrans 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.

Trispiropyrans provide an unusual synthetic challenge, so in the next step, methodology for synthesis of dispiropyrans was applied to prepare trispiropyrans. 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 method[16] for reductive coupling of carbonyl compounds to olefins with using of $AlCl_3$ 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 trispiropyrans **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 $ZnCl_2$ or $CoCl_2$ 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.

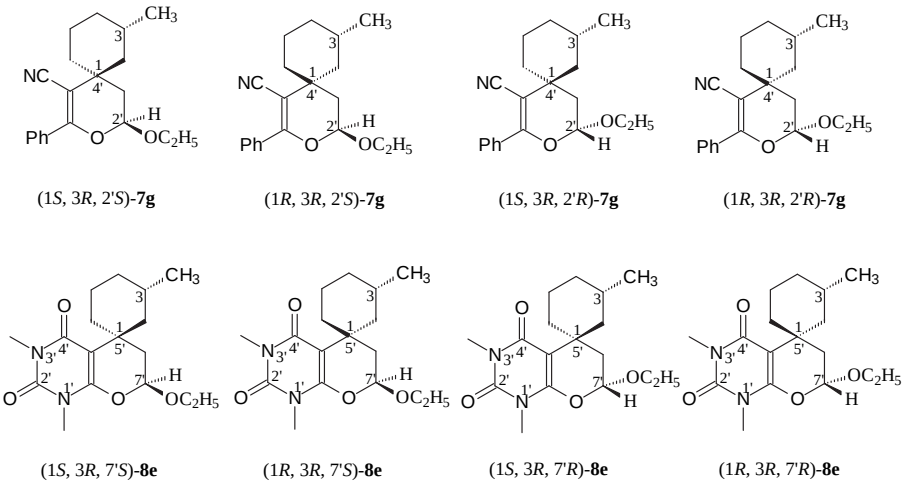
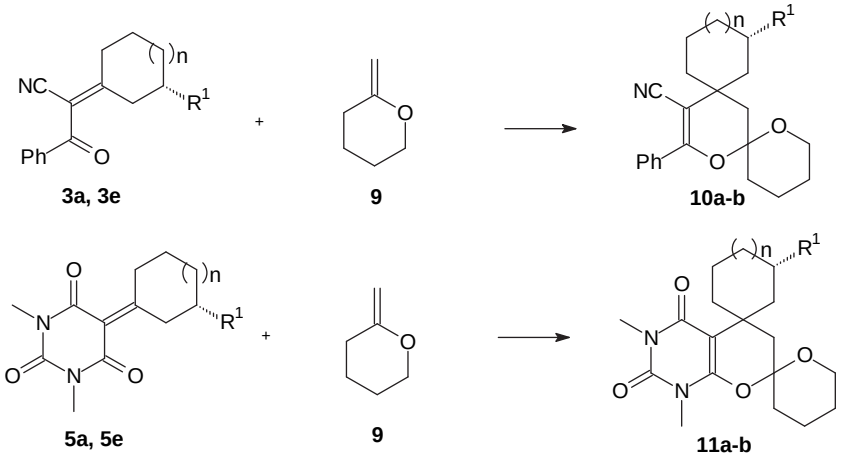


Fig. 2. Diastereoisomers of spiropyrans **7g** and **8e**.



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	*n*	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 $E_{LUMO}(H)-E_{HOMO}(D)$ 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

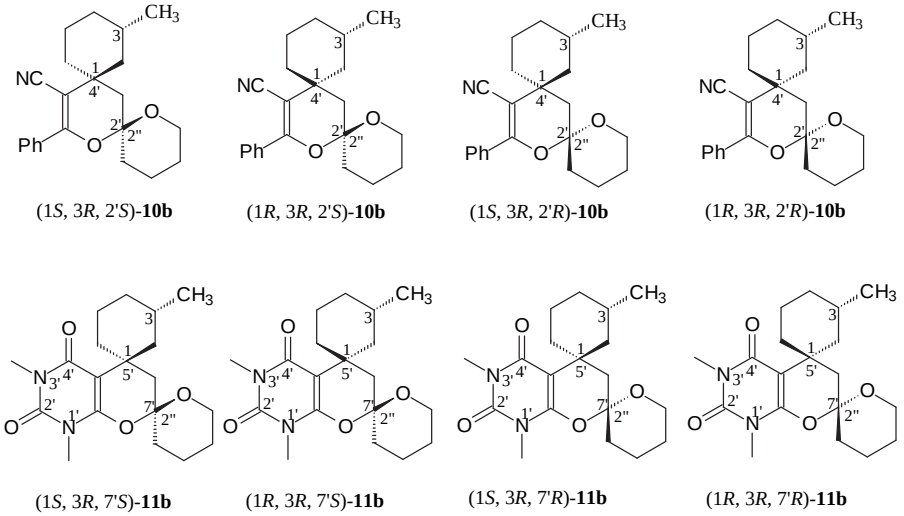
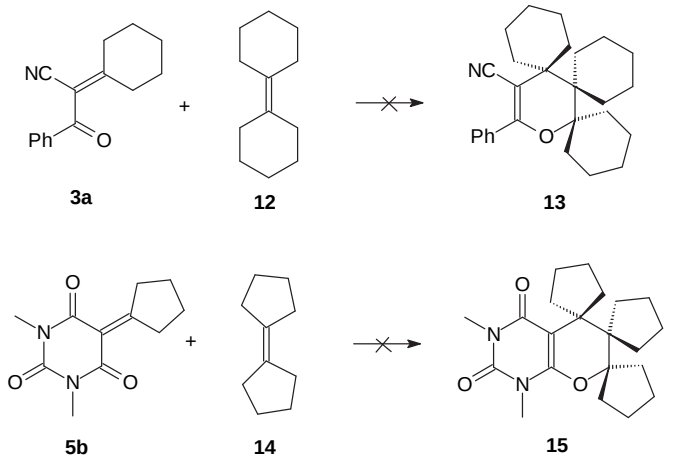


Fig. 3. Diastereoisomers of dispiropyrans **10b** and **11b**.



Scheme 4. Diels–Alder reactions of cycloalkylidene derivatives **3a**, **5b** with cycloalkylidenecycloalkane **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 $E_{LUMO}(H)-E_{HOMO}(D)$ 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 benzoylacetonitrile **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 cycloalkylidenecycloalkanes **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 $E_{LUMO}(H)-E_{HOMO}(D)$	Method PM3 $E_{LUMO}(H)-E_{HOMO}(D)$	Method HF/3-21G $E_{LUMO}(H)-E_{HOMO}(D)$
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 benzoylacetonitrile and *N*,*N*′-dimethylbarbituric acid were studied. Potential heterodienes were synthesized in 77–87% yields by Knoevenagel condensation of benzoylacetonitrile 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-methylenetetrahydropyrane, were performed in toluene solution at reflux and the spiropyrans 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 $E_{LUMO}(H)-E_{HOMO}(D)$ for reaction of ethyl-vinyl ether are slightly lower for the cycloalkylidene derivatives of *N*,*N*′-dimethylbarbituric acid than for the cycloalkylidene derivatives of benzoylacetonitrile. 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 (^{1}H: 300.18 MHz, ^{13}C: 75.48 MHz) in $CDCl_3$ with TMS as an internal standard. Mass spectra: Finningan Mat 95 (70 eV). Microanalyses were performed with Euro EA 3000 Elemental Analyzer.

4.2. Materials

Benzoylacetonitrile **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-methyl-cyclohexanone **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%]; $[\alpha]_D^{22}$ −13.1 (*c* 0.08, $CHCl_3$); ν_{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; ν_{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; ν_{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; ν_{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; ν_{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; ν_{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, OC*H*$_2$CH$_3$), 3.70 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{21}H_{27}NO_2$ 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, $CDCl_3$) 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, OC*H*$_2$CH$_3$), 3.68 (1H, dq, *J* 7.2, 9.6 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{20}H_{25}NO_2$ 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}; $[\alpha]_D^{22}$ −34.2 (*c* 0.12, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 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, OC*H*$_2$CH$_3$), 3.68 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 0.91 (3H, d, *J* 6.6 Hz, 3-Me); δ_C (75.5 MHz, $CDCl_3$) 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 BF_3Et_2O (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. $C_{20}H_{25}NO_2$ 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}; $[\alpha]_D^{22}$ −27.2 (*c* 0.12, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 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, OC*H*$_2$CH$_3$), 3.68 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 0.89 (3H, d, *J* 6.6 Hz, 3-Me); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{16}H_{24}N_2O_4$ 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, $CDCl_3$) 5.13 (1H, dd, *J* 2.1, 8.4 Hz, 7′-H), 3.99 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 3.69 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{15}H_{22}N_2O_4$ 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, $CDCl_3$) 5.08 (1H, dd, *J* 2.1, 8.1 Hz, 7′-H), 3.93 (1H, dq, *J* 7.2, 9.6 Hz, OC*H*$_2$CH$_3$), 3.65 (1H, dq, *J* 7.2, 9.6 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{17}H_{26}N_2O_4$ 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, $CDCl_3$) 5.18 (1H, dd, *J* 2.1, 8.7 Hz, 7′-H), 4.00 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 3.71 (1H, dq, *J* 7.2, 9.3 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{18}H_{28}N_2O_4$ 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, $CDCl_3$) 5.20 (1H, dd, *J* 2.4, 8.7 Hz, 7′-H), 4.00 (1H, dq, *J* 7.2, 9.6 Hz, OCH_2CH$_3$), 3.70 (1H, dq, *J* 7.2, 9.6 Hz, OCH_2CH$_3$), 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, OCH$_2$CH_3); δ_C (75.5 MHz, $CDCl_3$) 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. $C_{17}H_{26}N_2O_4$ requires C, 63.33; H, 8.13; N, 8.69%]; R_f (1:2 EtOAc/pet. ether) 0.36; $[\alpha]_D^{22}$ −42.3 (*c* 0.21, $CHCl_3$); ν_{max}(film) 2967, 2909, 2868, 2850, 1706, 1648, 1157 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.99 (1H, dd, *J* 2.4, 8.7 Hz, 7′-H), 3.92 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH$_3$), 3.63 (1H, dq, *J* 7.2, 9.3 Hz, OCH_2CH$_3$), 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, OCH$_2$CH_3), 0.97 (3H, d, *J* 7.2 Hz, 3-Me); δ_C (75.5 MHz, $CDCl_3$) 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 BF_3Et_2O (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. $C_{17}H_{26}N_2O_4$ requires C, 63.33; H, 8.13; N, 8.69%]; R_f (1:2 EtOAc/pet. ether) 0.43; $[\alpha]_D^{22}$ −31.5 (*c* 0.21, $CHCl_3$); ν_{max}(film) 2969, 2912, 2863, 2848, 1701, 1644, 1149 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.23 (1H, dd, *J* 2.4, 7.5 Hz, 7′-H), 3.97 (1H, dq, *J* 7.2, 9.6 Hz, OCH_2CH$_3$), 3.69 (1H, dq, *J* 7.2, 9.6 Hz, OCH_2CH$_3$), 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, OCH$_2$CH_3), 1.03 (3H, d, *J* 7.2 Hz, 3-Me); δ_C (75.5 MHz, $CDCl_3$) 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-methylenetetrahydropyrane **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. $C_{21}H_{25}NO_2$ 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, $CDCl_3$) 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 tetrahydropyrane); δ_C (75.5 MHz, $CDCl_3$) 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-methylenetetrahydropyrane **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. $C_{22}H_{27}NO_2$ requires C, 78.30; H, 8.06; N, 4.15%]; R_f (1:2 EtOAc/pet. ether) 0.51; $[\alpha]_D^{22}$ −74.5 (*c* 0.13, $CHCl_3$); ν_{max}(KBr) 2949, 2915, 2869, 2195, 1588, 1152 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72–7.69 (2H, m, Ph), 7.43–7.41 (3H, m, Ph), 0.89 (3H, d, *J* 6.3 Hz, 3-CH$_3$), 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 tetrahydropyrane), 2.21–2.12 (1H, m, 3′-H), 1.99–1.57 (12H, m, cyclohexane, and tetrahydropyrane), 1.99–1.07 (1H, m, cyclohexane, and tetrahydropyrane), 1.45–1.34 (1H, m, cyclohexane, and tetrahydropyrane); δ_C (75.5 MHz, $CDCl_3$) 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-methylenetetrahydropyrane **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. $C_{18}H_{26}N_2O_4$ 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, $CDCl_3$) 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–CH$_3$), 3.32 (3H, s, N–CH$_3$), 2.77 (1H, m, cyclohexane or tetrahydropyrane), 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 tetrahydropyrane); δ_C (75.5 MHz, $CDCl_3$) 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′,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-methylenetetrahydropyrane **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. $C_{19}H_{28}N_2O_4$ requires C, 65.49; H, 8.10; N, 8.04%]; R_f (1:2 EtOAc/pet. ether) 0.41; $[\alpha]_D^{22}$ −63.2 (*c* 0.15, $CHCl_3$); ν_{max}(film) 2946, 2915, 2870, 1701, 1638, 1623, 1167, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 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 tetrahydropyrane), 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 tetrahydropyrane), 0.96 (3H, d, *J* 7.2 Hz, 3-Me); δ_C (75.5 MHz, $CDCl_3$) 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).

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