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PII: S0040-4020(19)30299-6

DOI: https://doi.org/10.1016/j.tet.2019.03.024

Reference: TET 30210

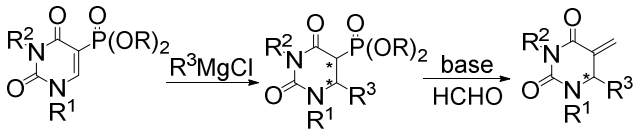
To appear in: *Tetrahedron*

Received Date: 25 January 2019

Revised Date: 25 February 2019

Accepted Date: 12 March 2019

Please cite this article as: Pięta M, Kędzia J, Kowalczyk D, Wojciechowski J, Wolf WM, Janecki T, Enantioselective synthesis of 5-methylidenedihydrouracils as potential anticancer agents, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.03.024.



R = Et, (*R*)- or (*S*)-1-phenylethylamine ee ≥ 98%

Enantioselective synthesis of 5-methylidenedihydrouracils as potential anticancer agents

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ABSTRACT

An efficient, versatile, enantioselective synthesis of 1,3-disubstituted and 1,3,6-trisubstituted 5-methylidenedihydrouracils applying Horner-Wadsworth Emmons methodology was developed. Starting 1,3-disubstituted 5-diethoxyphosphoryluracils were subjected to reduction of the double bond or addition of various Grignard reagents and obtained Horner-Wadsworth Emmons reagents were used for the olefination of formaldehyde. Enantioselective synthesis of 1,3,6-trisubstituted 5-methylidenedihydrouracils was accomplished by introducing (*R*,*R*)- or (*S*,*S*)-di(1-phenylethylamino)phosphoryl groups as chiral auxiliary. Additions of Grignard reagents in the presence of these groups were highly and complimentary diastereoselective (de ~ 80%). Further separation of the diastereomeric mixtures by column chromatography enabled synthesis of (*R*)- and (*S*)-1,3,6-trisubstituted-5-methylidenedihydrouracils with ee ≥ 98%. Furthermore, absolute configuration of the adducts and final products was established using single crystal X-ray analysis. Stereochemical course of the addition reactions is also discussed.

Keywords: methylidenedihydrouracils; Michael addition; Horner-Wadsworth-Emmons reaction; enantioselective synthesis

1. Introduction

Uracyl **1** is one of natural pyrimidine nucleoside bases and is regarded as one of the most important pharmacophore moieties. Uracyl skeleton is present in many drugs possessing wide spectrum of bioactivity, such as HIV-1 non-nucleoside reverse transcriptase inhibitor 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) **2**[1] or antibiotic sparsomicin **3**[2]. Moreover, it is a core structure in many drugs used in the treatment of cancer which are pyrimidine antimetabolites.[3] Representative examples are 5-fluorouracil **4** (Figure 1) and various modifications of this structure with enhanced pharmacological properties, such as 5-fluorodeoxyuridine or thiarabine. Uracyl skeleton is also present in several compounds exhibiting high cytotoxic activity, including long chained 2-uracil-3-yl-N(4-phenoxyphenyl)acetamides[4] or products of the reaction between 6-amine-1,3-dimethyluracil and *bis*-chalcones[5]. Furthermore, synthesis of compounds with uracyl ring conjugated with other bioactive pharmacophores, such as 1H-indole-2,3-dione[6] or camptothecin[7] has been reported and obtained hybrids showed promising cytotoxic activity.

From some time, great attention is given to 5-methylidenedihydrouracils **5** because they are considered the intermediates in the production of thymidyl moieties by methylation of uridyl moieties.[8] Possible mechanisms of this biological transformation has been studied and successful attempts to trap this methylidene intermediate by 2-mercaptoethanol in thymidylate synthase (Ts) catalyzed reaction[9] or by water in flavin-dependent thymidylate synthase (FDTS) catalyzed reaction[10], was reported. Also, it was demonstrated, that 5-phenylselenide[11,12] or 5-methylselenide[13] modified thymidines, under oxidation conditions, are readily converted to electrophilic 5-methylidene-6-(phenyl- or methylselenyloxy)uridines **6**, *via* [2,3]-sigmatropic rearrangement, and act as anticancer

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alkylating agents by formation of interstrand cross-links. In this respect, very recently, the synthesis of C-5 olefin isomer of thymidylate (5-methylidene-5,6-dihydrouridylphosohate) has been reported to enhance studies of enzyme reaction mechanisms and serve as templates for rational drug design.[14]

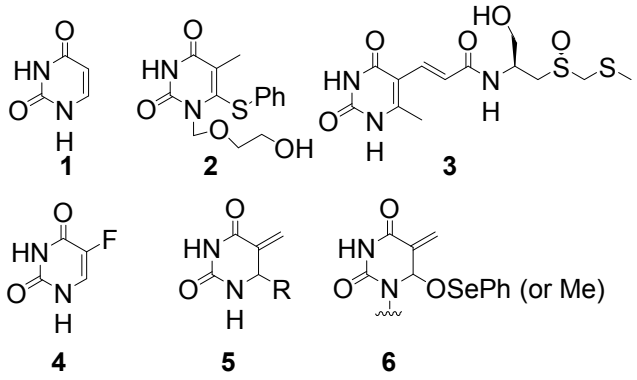


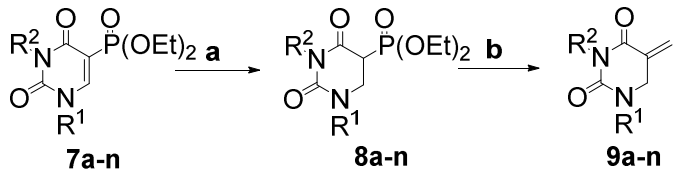
Figure 1. Structures of biologically active compounds containing uracil skeleton.

Presented data show that 5-methylidene-5,6-dihydrouracil moiety **5** has a great potential as pharmacophoric group with anticancer properties. This group contains conjugated *exo*-methylidene double bond incorporated onto the dihydrouracyl ring what rises the possibility of enhanced cytotoxic activity of the obtained hybrid, as it may act as pyrimidine antimetabolite and/or as alkylating agent. Surprisingly there are only few reports on the synthesis of compounds containing this moiety. And so, 1,3-disubstituted 5-methylidenedihydrouracils were obtained from 2-(bromomethyl)acrylic acid and symmetrically or unsymmetrically substituted carbodiimides[15] whereas enantiomerically enriched 1,3,6-trisubstituted 5-methylidenedihydrouracils were obtained in nickel catalysed [2+2+2] cycloaddition reaction of monosubstituted allenes possessing a primary alkyl group with aryl isocyanates.[16] Also, synthesis of 5-arylidene-5,6-dihydrouracils have been reported.[17,18] Surprisingly, none of the synthesized compounds have been tested for the biological activity, for example cytotoxicity.

In continuation of our search for new anticancer drugs, herein we present new, versatile, efficient and enantioselective synthesis of alkyl or aryl 1,3-disubstituted 5-methylidenedihydrouracils **9** and 1,3,6-trisubstituted 5-methylidenedihydrouracils **11**, applying, elaborated in our laboratory, Horner-Wadsworth-Emmons methodology.[19,20]

2. Results and discussion

We started our studies with the synthesis of 1,3-disubstituted-5-methylidenedihydrouracils **9** (Scheme 1). Starting 1,3-disubstituted-5-diethoxyphosphoryluracils **7a-n** were prepared applying procedure developed recently in our laboratory.[21] Uracils **7a-n** were subjected to reduction of carbon-carbon double bond. Two methods were examined in which L-selectride or sodium borohydride were used as reducing agents. The first procedure proved to be superior and all expected 1,3-disubstituted-5-diethoxyphosphoryldihydrouracils **8a-n** were obtained in high yields (Table 1). Using Horner-Wadsworth-Emmons methodology 5-diethoxyphosphoryldihydrouracils **8a-n** were next transformed efficiently into 1,3-disubstituted-5-methylidenedihydrouracils **9a-n** using formalin as a source of formaldehyde and potassium carbonate as base.



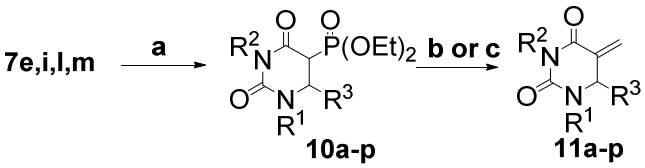
Scheme 1 Conditions : (a) L-Selectride, THF, -78 °C → 0°C, 2 h (b) 37% CH_2O_{aq}, K_2CO_3, THF, H_2O, 60 min, 0°C → rt.

Table 1. Synthesis of 1,3-disubstituted-5-diethoxyphosphoryldihydrouracils **8a-n** and 1,3-disubstituted-5-methylidenedihydrouracils **9a-n**

Compound	R^1	R^2	**8** Yield[a] [%]	**9** Yield[a] [%]
a	Me	*n*-Bu	81	81
b	4-$MeOC_6H_4$	*n*-Bu	82	78
c	*c*-Hexyl	*c*-Hexyl	83	75
d	Me	*c*-Hexyl	84	80
e	Et	Ph	88	73
f	*c*-Hexyl	4-MeC_6H_4	88	72
g	Et	4-MeC_6H_4	87	83
h	Me	4-MeC_6H_4	87	80
i	Et	4-$MeOC_6H_4$	86	76
j	Me	4-$MeOC_6H_4$	84	86
k	4-$MeOC_6H_4$	4-BrC_6H_4	82	95
l	Et	4-BrC_6H_4	85	82
m	Me	4-$Me_2NC_6H_4$	88	88
n	Me	2-Pyridyl	90	45

[a] Yield of pure, isolated product, based on **7** or **8**, respectively.

To broaden the scope of this methodology we decided to prepare 6-methylidenedihydrouracils containing additional substituent in position 6. To achieve this goal selected 1,3-disubstituted uracils **7e,i,l,m** were used as Michael acceptors in the reaction with various Grignard reagents. The additions proceeded smoothly and series of 1,3,6-trisubstituted-5-diethoxyphosphoryldihydrouracils **10a-p** was obtained efficiently in 76 - 96% yields (Scheme 2, Table 2). All adducts were obtained as *trans* diastereoisomers exclusively. Configurational assignments were made on the basis of diagnostic $^3J_{H5H6}$ coupling constants which fell in the range between 1.0 Hz and 1.3 Hz. Similar coupling constants, characteristic for *trans* diaxial arrangement of diethoxyphosphoryl group and substituent in position 4 were observed in 4-substituted trans-3-diethoxyphosphorylchroman-2-ones[22,23,24] and 4-substituted *trans*-3-diethoxyphosphorylquinolin-2-ones[19]. In the next step, 5-diethoxyphosphoryldihydrouracils **10a-p** were transformed into 1,3,6-trisubstituted-5-methylidenedihydrouracils **11a-p** applying Horner-Wadsworth-Emmons olefination. 5-Methylidenedihydrouracils **11a-c,e-g,i-k,m-o** containing aliphatic substituents in position 6 were obtained effectively using paraformaldehyde in the presence of NaH (Table 2). Unfortunately, when 5-diethoxyphosphoryldihydrouracils **10d,h,l,p** possessing phenyl group in position 6 were subjected to these olefination conditions, complex reaction mixtures were obtained. However, changing the reaction conditions and using formalin in the presence of K_2CO_3 as base gave desired 6-phenyl-5-methylidenedihydrouracils **11d,h,l,p** in good yields (61-75%).



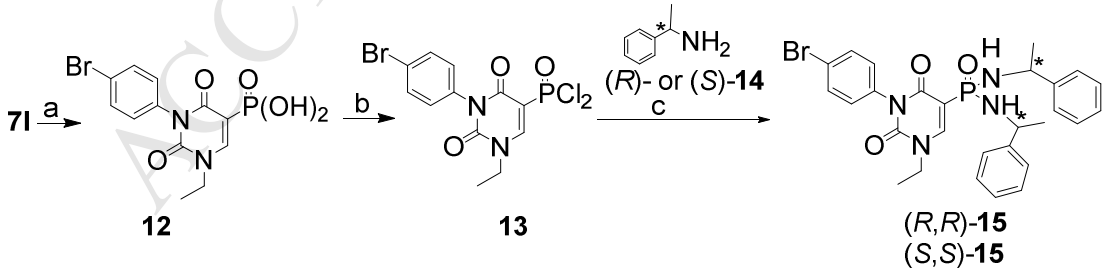
Scheme 2 Conditions: (a) R^3MgCl, THF, 60 min, rt; (b) $(CH_2O)_n$ (5 eq), NaH (1.1 eq), THF, 60 min, rt (c) 37% CH_2O_{aq} (10 eq), K_2CO_3 (2 eq), THF, H_2O, 30 min, 0°C → rt.

Table 2. Synthesis of 1,3,6-trisubstituted 5-diethoxyphosphorylodihydrouracils **10a-p** and 1,3,6-trisubstituted 5-methylidenedihydrouracils **11a-p**

Compound	R^1	R^2	R^3	**10** Yield[a] [%]	**11** Yield[a] [%]
a	Et	Ph	Me	92	81
b	Et	Ph	Et	95	95
c	Et	Ph	*i*-Pr	93	97
d	Et	Ph	Ph	83	75
e	Et	4-$MeOC_6H_4$	Me	75	77
f	Et	4-$MeOC_6H_4$	Et	93	96
g	Et	4-$MeOC_6H_4$	*i*-Pr	92	92
h	Et	4-$MeOC_6H_4$	Ph	91	74
i	Et	4-BrC_6H_4	Me	89	82
j	Et	4-BrC_6H_4	Et	86	97
k	Et	4-BrC_6H_4	*i*-Pr	76	98
l	Et	4-BrC_6H_4	Ph	94	61
m	Me	4-$Me_2NC_6H_4$	Me	96	83
n	Me	4-$Me_2NC_6H_4$	Et	96	87
o	Me	4-$Me_2NC_6H_4$	*i*-Pr	92	91
p	Me	4-$Me_2NC_6H_4$	Ph	93	68

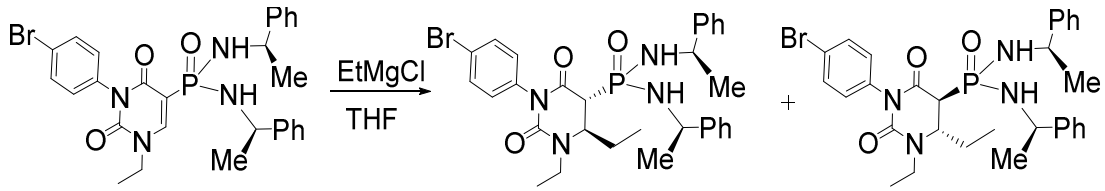
[a] Yield of pure, isolated product, based on **9** or **10**, respectively.

To demonstrate that presented methodology can be also applied for the synthesis of non-racemic 5-methylidenedihydrouracils **11**, we decided to utilize di(1-phenylethylamino)phosphoryl group as chiral auxiliary, which, very recently, proved to be effective in the synthesis of enantiomeric 3-methylidenequinolin-2-ones.[25] In this respect, taking into account preliminary biological screening of the obtained racemic 5-methylidenedihydrouracils **11**, which showed significant cytotoxic activity of 3-(4-bromophenyl)-1-ethyl-5-methylidenedihydrouracils **11i-l**, we decided to synthesize (*R*,*R*)- and (*S*,*S*)-3-(4-bromophenyl)-1-ethyl-5-di(1-phenylethylamino)phosphoryluracils (*R*,*R*)- and (*S*,*S*)-**15** in a three step reaction sequence shown in Scheme 3. In the first step selected phosphonate **7l** was hydrolyzed to phosphonic acid **12** performing the reaction with TMSBr and then with MeOH. Next, using oxalyl chloride, phosphonic acid **12** was converted into dichloride **13**, which in the reaction with enantiomerically pure (*R*)- or (*S*)-1-phenylethylamine (*R*)- or (*S*)-**14** in the presence of TEA gave expected uracils (*R,R*) and (*S,S*)-**15** in high 85% and 88% yields after three steps, respectively.



Scheme 3 Conditions: (a) 1) TMSBr, CH_2Cl_2, 20 h, rt; 2) MeOH; (b) $(COCl)_2$, cat. DMF, CH_2Cl_2, 90 min, reflux; (c) TEA, CH_2Cl_2, 20 h, rt.

With both enantiomeric 5-di(1-phenylethylamino)phosphoryluracils (*R*,*R*)- and (*S*,*S*)-**15** in hand we performed addition of Grignard reagents to these Michael acceptors. To find optimal conditions for this transformation, the addition of ethylmagnesium chloride to uracil (*R*,*R*)-**15** was performed as model reaction (Scheme 4). Results are shown in Table 3.



(*R*,*R*)-**15** (5*R*,6*R*)-**16b** (5*S*,6*S*)-**16b**

Scheme 4 Model reaction of (*R*,*R*)-5-di(1-phenylethylamino)phosphoryluracil (*R*,*R*)-**15** with ethylmagnesium chloride.

Table 3. Optimalization of the addition of ethylmagnesium chloride to uracil (*R,R*)-**15**.

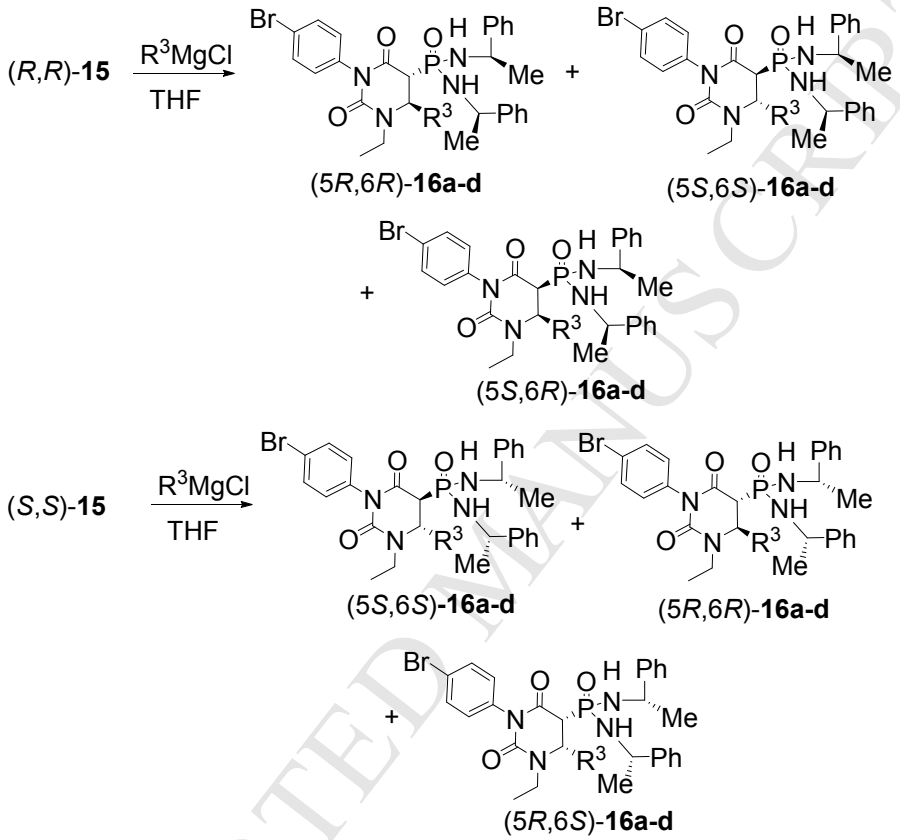
Entry	Solvent	Temp.(°C)	Eq of EtMgCl	Ratios of (5*R*,6*R*)-**16b** to (5*S*,6*S*)-**16b**[a]	Conversion (%)[b]
1	THF	20	4	88:12	95
2	2-MeTHF	20	4	75:25	90
3	Et_2O	20	4	69:31	97
4	Dioxane	20	4	76:24	58
5	CH_2Cl_2	20	4	60:40	93
6	Toluene	20	4	73:27	96
7	THF	0	4	89:11	76
8	THF	0	5	89:11	97
9	THF	0	6	89:11	100
10	THF	-15	6	90:10	100
11	THF	-40	7	90:10	83
12	THF	-78	7	91:9	59

[a] Ratios taken from the integration of ^{31}P NMR spectra.
[b] Conversion of (*R*,*R*)-**15** to (5*R*,6*R*)-**16b** and (5*S*,6*S*)-**16b**. Taken from the integration of ^{31}P NMR spectra.

In all experiments two diasteroisomeric *trans*-adducts (5*R,*6*R*)-**16b** and (5*S,*6*S*)-**16b** were obtained. Screening of the solvents proved superiority of THF over other selected ethers, dichloromethane or toluene in terms of diastereoselectivity (Table 3, entry 1-6). Full conversion of the substrate (*R,R*)-**15** demanded bigger excess of Grignard reagent (entry 7-9). Gradual decreasing of the temperature to -78 °C gave little improvement in diastereoselectivity and at the same time substantial reduction of conversion (entry 10-12). Attempts to improve results of the reaction conducted in THF by addition of different activators, such as CuI, Et_2O*BF_3 or TMSOTf proved futile. Summing up the obtained results, we decided to perform the additions applying conditions shown in the entry no. 10.

Addition of methylmagnesium chloride to (*R*,*R*)**-** and (*S*,*S*)-**15** in the optimized conditions led in each case to the formation of three diastereoisomers, i.e. two *trans*-adducts (5*R*,6*R*)- and (5S,6S)-**16a** and *cis*-adduct (5*S*,6*R*)-**16a** in 74 : 10 : 16 ratio and two *trans*-adducts (5*S*,6*S*)- and (5*R*,6*R*)-**16a** and *cis*-adduct (5*R*,6*S*)-**16a** in 73 : 10 : 17 ratio, respectively (Scheme 5, Table 4). It is worth to stress that both *cis*-adducts (5*S*,6*R*)-**16a** and (5*R*,6*S*)-**16a** had the same absolute configuration in position 6 as major *trans*-adducts (5*R*,6*R*)-**16a** and (5S,6S)-**16a**, respectively (vide infra). On the other hand, addition of ethyl, isopropyl and phenylmagnesium chlorides to (*R*,*R*)**-** and (*S*,*S*)-**15** proceeded with higher diastereoselectivity and only *trans*-adducts were formed. The reaction with (*R*,*R*)-**15** furnished

adducts (5*R*,6*R*)- and (5S,6S)-**16b-d** in ratios between 88 : 12 to 90 : 10, whereas the reaction with (*S*,*S*)-**15** furnished adducts (5*S*,6*S*)- and (5*R*,6*R*)-**16b-d** in ratios between 88 : 12 to 91 : 9, respectively. Interestingly, the reactions with (*R,R*)-**15** and (*S,S*)-**15** proceed with opposite diastereoselectivity giving (5*R*,6*R*)-**16b-d** or (5*S*,6*S*)-**16b-d** as major diastereoisomers, respectively. Purification of the crude products by column chromatography enabled the enrichment of the mixtures in the predominant diastereoisomer. These enriched products were obtained in 53-60% yield, with dr up to >99:1 (Table 4, ratios in the brackets) and were used in the next step.



Scheme 5 Synthesis of 3-({bis[(1-phenylethyl)amine]}phosphoryl)-3-(4-bromophenyl)-1-ethyl-dihydrouridines **16a-d**.

Table 4. Synthesis of 3-({bis[(1-phenylethyl)amine]}phosphoryl)-3-(4-bromophenyl)-1-ethyl-dihydrouridines **16a-d**.

16	**15**	**R^3**	Ratio of (5*R*,6*R*)-**16** to (5*S*,6*S*)-**16** to (5*S*,6*R*)-**16** to (5*R*,6*S*)-**16**[a]	Yield (%)[b]
a	*(R,R)*	Me	74:10:16:0 (94:0:6:0)	50
b	*(R,R)*	Et	90:10:0:0 (>99:1:0:0)	57
c	*(R,R)*	*i*-Pr	89:11:0:0 (>99:1:0:0)	60
d	*(R,R)*	Ph	88:12:0:0 (>99:1:0:0)	54
a	*(S,S)*	Me	10:73:0:17 (0:93:0:7)	53
b	*(S,S)*	Et	10:90:0:0 (<1:99:0:0)	59
c	*(S,S)*	*i*-Pr	9:91:0:0 (<1:99:0:0)	58
d	*(S,S)*	Ph	12:88:0:0 (<1:99:0:0)	53

[a] Ratios taken from the integration of ^{31}P NMR and ^{1}H NMR spectra. In brackets ratios after purification and separation by column chromatography.

[b] Yield after separation and purification by column chromatography, based on **15**.

Relative configuration of the addition products **16a-d** was established on the basis of ^{1}H NMR spectra. Like in the case of racemic adducts **10** diagnostic were $^{3}J_{H5H6}$ coupling constants. In *trans*-diastereoisomers **16a-d** $^{3}J_{H5H6}$ coupling constants were in the range of 1.0 – 1.1 Hz whereas in *cis*-diastereoisomers **16a** $^{3}J_{H5H6}$ had value of 5.0 Hz. To assign the absolute configuration of the obtained adducts **16** single crystal X-ray structure of (5*R*,6*R*)-3-[(bis{[(1*R*)-1-phenylethyl]amine})phosphoryl]-3-(4-bromophenyl)-1-ethyl-6-phenyl-dihydrouracil (5*R*,6*R*)**-16d** was determined (Figure 2). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1877237. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). This experiment confirmed the assumption from the NMR analysis, that Michael addition of Grignard reagents to uracils **15** gives *trans*-adducts as a main products and also enabled the assignment of *R* absolute configuration to C-6 stereogenic center in (5*R*,6*R*)-**16d**. We believe that this conclusion can be generalized and Michael additions of Grignard reagents to (*R*,*R*)- and (*S*,*S*)-uracils **15** give (5*R*,6*R*)- or (5*S*,6*S*)-dihydrouracils **16a-d** as major diastereoisomers, respectively.

Consequently, addition of Grignard reagents to (*R*,*R*)-**15** takes place preferentially from the *Re*-face and to (*S*,*S*)-**15** from the *Si*-face of the C-6 carbon atom. Formation of the more stable *trans*-adducts as a major or the only products of the addition can be rationalized assuming equilibration at the C-5 chiral center in strongly basic conditions. Formation of the *cis*-adducts (5*S*,6*R*)-**16a** and (5*R*,6*S*)-**16a** in the addition of methylmagnesium chloride to (*R*,*R*)**-** and (*S*,*S*)-**15** are most probably the consequence of relatively small steric hindrance of methyl group in comparison to ethyl, isopropyl or phenyl groups. However, preferred stereoselectivity of the addition is maintained and takes place from the *Re*- or *Si*-face, respectively.

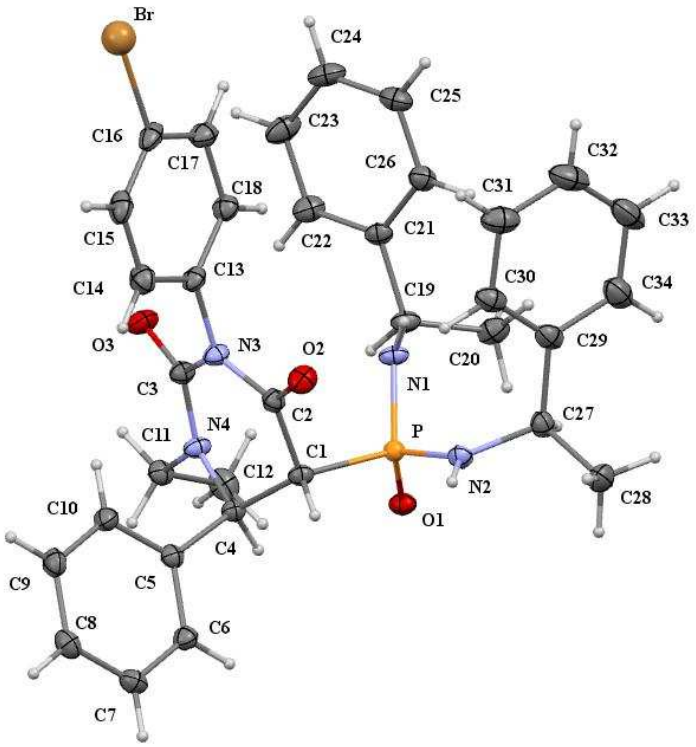
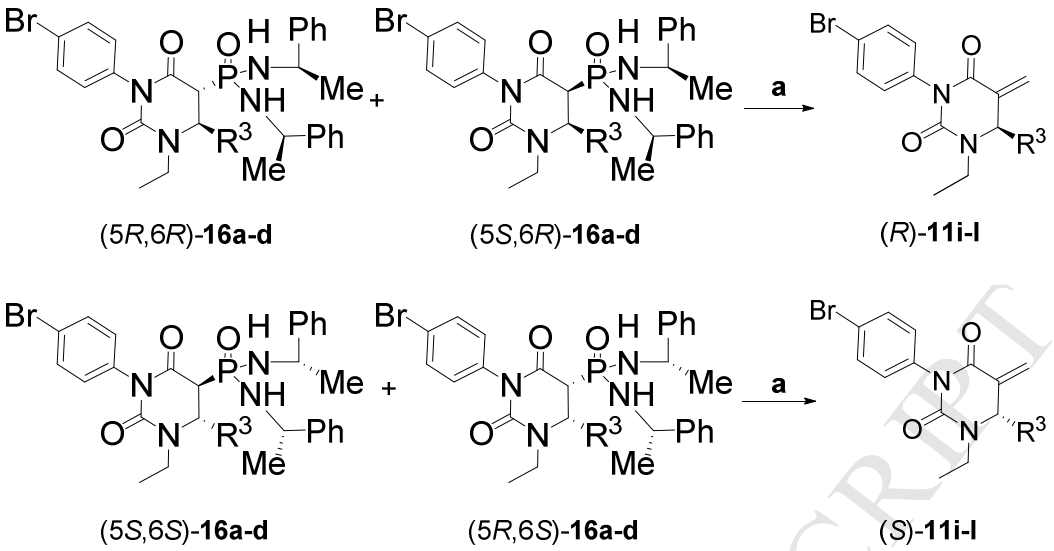


Figure 2. View of the (5*R*,6*R*)-3-[(bis{[(1*R*)-1-phenylethyl]amine})phosphoryl]-3-(4-bromophenyl)-1-ethyl-6-phenyldihydrouracil (5*R*,6*R*)-**16d** molecule. Displacement ellipsoids are drawn at the 50% probability level, hydrogen atoms are represented by circles of an arbitrary radius, the co-crystallized water molecule has been omitted for clarity.

In the final step Horner-Wadsworth-Emmons olefination of formaldehyde using obtained adducts **16a-d** was accomplished (Scheme 6). These reactions were performed in the conditions used in the synthesis of the respective racemates. After purification by column chromatography (*R*)- or (*S*)-5-methylidenedihydrouracils **11i-l** were obtained in 51-89% yields with enanctiomeric excesses from 98% to >99% (Table 5). Spectroscopic data for these compounds were identical as these registered for the corresponding racemates. Because configuration of the C-6 chiral centers is certainly preserved during Horner-Wadsworth-Emmons olefination, therefore final 4-methylidenedihydrouracils **11i-l** should have the same configuration at this center as corresponding starting dihydrouracils **16a-d**. It is also worth to notice that, while dihydrouracils **16b-d** used in HWE olefination were single diastereoisomers, dihydrouracils **16a** were mixtures of *trans*- and *cis*-diastereoisomers in 94 : 6 or 93 : 7 ratio. The fact that final (*R*)- or (*S*)- methylideneuracils **11i** have ee ≥ 99% proves that the corresponding *cis*-dihydrouracils **16a** have the same absolute configuration on C-6 chiral center as *trans*-dihydrouracils **16a** present in the mixtures.



Scheme 6 Conditions: $(CH_2O)_n$, NaH, THF, rt or 37% CH_2O_{aq}, K_2CO_3, THF, H_2O, 0°C.

Table 5. Synthesis of nonracemic 1,3,6-trisubstituted-5-methylidenedihydrouracils **11**

Compound	R^3	ee[a] (%)	Yield[b] (%)
(*R*)-**11i**	Me	>99	83
(*R*)-**11j**	Et	>99	80
(*R*)-**11k**	*i*-Pr	99	81
(*R*)-**11l**	Ph	>99	51
(*S*)-**11i**	Me	99	87
(*S*)-**11j**	Et	>99	89
(*S*)-**11k**	*i*-Pr	98	79
(*S*)-**11l**	Ph	>99	59

[a]Enantiomeric excesses determined by chiral HPLC analysis of isolated products.
[b]Yield of pure, isolated product based on **16**.

3. Conclusions

Presented data clearly show that Horner-Wadsworth-Emmons methodology can be effectively applied in the synthesis of both alkyl and aryl 1,3-disubstituted as well as 1,3,6-trisubstituted 5-methylidenedihydrouracils **9** and **11**. Furthermore, it was demonstrated that diethoxyphosphoryl group in starting 5-diethoxyphosphoryluracil **7l** can be easily transformed into (*R*,*R*)- or (*S*,*S*)-di(1-phenylethylamino)phosphoryl group and Grignard additions performed in the presence of these chiral auxiliary groups are highly diastereoselective and occur with opposite diastereoselectivity. Consequently, after trivial separation of the obtained diastereoisomeric mixtures by column chromatography, pure diastereoisomers can be isolated and used in Horner-Wadsworth-Emmons olefination of formaldehyde to give enantiomeric (*R*)- and (*S*)-1,3,6-trisubstituted-5-methylidenedihydrouracils **11i-l** with ee ≥ 98%. Furthermore, determination of the absolute configuration of the adduct (5*R*,6*R*)-**16d** by single crystal X-ray structure analysis enabled us to establish the stereochemical course of the addition reactions. We found that Grignard additions to (*R*,*R*)-**15** takes place preferentially from the *Re*-face and to (*S*,*S*)-**15** from the *Si*-face of the C-6 carbon atom. These results confirmed great utility of (*R*,*R*)- or (*S*,*S*)-di(1-phenylethylamino)phosphoryl group, as chiral auxiliary. It is worth to stress that this group was very recently introduced in our laboratory and sucessfuly applied in the enantioselective synthesis of both enantiomers of 1,4-disubstituted 3-methylidenedihydroquinolin-2(1*H*)-ones.[25] Currently, additional investigations, including

computational studies, to rationalize stereochemical outcome of the additions carried out with (*R*,*R*)- and (*S*,*S*)-di(1-phenylethylamino)phosphoryl group as chiral auxiliary, are in progress.

As it was stated in the introduction, 5-methylidenedihydrouracils are potential cytotoxic agents. Therefore, cytotoxicity and other biological tests of the obtained final products are currently performed and preliminary results show that some of them have very high and promising activity. These biological results will be reported very shortly.

Experimental

General information

NMR spectra were recorded on a Bruker DPX 250 or Bruker Avance II instrument at 250.13 MHz or 700 MHz for 1H, 62.9 MHz or 176 MHz for 13C, and 101.3 MHz for 31P NMR using tetramethylsilane as internal and 85% H3PO4 as external standard. 31P NMR spectra were recorded using broadband proton decoupling. IR spectra were recorded on a Bruker Alpha ATR spectrophotometer. Melting points were determined in open capillaries and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in $deg \cdot cm^2 \cdot g^{-1}$; concentration c is listed in $g \cdot (100\ mL)^{-1}$. Column chromatography was performed on Aldrich silica gel 60 (230–400 mesh). Thin-layer chromatography was performed with precoated TLC sheets of silica gel 60 F254 (Aldrich). The purity of tested compounds was determined by combustion elemental analyses (CHN, elemental analyzer EuroVector 3018, Elementar Analysensysteme GmbH). MS spectra were performed on combined Waters 2695-Waters ZQ 2000 LC/MS apparatus. The enantiomeric ratio (er) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IA, IC, ID columns). Reagents and starting materials were purchased from commercial vendors and used without further purification. All organic solvents were dried over appropriate drying agents and distilled prior to use. Standard syringe techniques were used for transferring dry solvents.

General procedure for the synthesis of *N,N'*-disubstituted-5-metylidenedihydrouracils 9a-n

To the solution of *N,N'*-disubstituted-5-diethoxyphosphorylodihydrouracil **7a-n** (0.5 mmol) i THF (2 mL) 36-38% water solution of formaldehyde (0.38 mL, ca. 5.0 mmol) was added at 0 °C. It was followed by addition of Na_2CO_3 (138 mg, 1.0 mmol) dissolved in water (2 mL). The resulting mixture was stirred at 0 °C for 30 min and after removal of the ice bath for additional 30 min. After addition of AcOEt (2 mL) the formed layers were separated. The water fraction was then washed with CH_2Cl_2 (3 mL). Organic fractions were combined and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting crude product was then purified by column chromatography (eluent CH_2Cl_2 : $CHCl_3$ or CH_2Cl_2 : AcOEt).

3-butyl-1-methyl-5-methylidene-1,3-diazinane-2,4-dione (9a) (79.5 mg, 81%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 5:1). Rf: 0.7 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2957, 2872, 1703, 1665, 1409, 1209, 1107. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.85 (t, 3H, *J* = 7.4 Hz), 1.26 (hept, 2H, *J* = 7.4 Hz), 1.43-1.54 (m, 2H), 2.96 (s, 3H), 3.90 (t, 2H, *J* = 7.7 Hz), 3.98 (d, 2H, *J* = 1.9, 1.8 Hz), 5.51 (dt, 1H, *J* = 1.9, 0.9 Hz), 6.27 (dt, 1H, *J* = 1.8, 0.9 Hz). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.76, 20.15, 30.48, 35.33, 41.02, 49.20, 123.81, 131.67, 153.05, 162.91. ESI-MS $[M+H]^+$ = 197. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20%, H, 8.22; N%, 14.27%. Found: C, 61.42%, H, 8.25%, N, 14.20%.

3-butyl-1-(4-methoxyphenyl)-5-methylidene-1,3-diazinane-2,4-dione (9b) (112 mg, 78%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 6:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2957, 1705, 1661, 1510, 1440, 1245, 1122, 1028. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.91 (t, 3H, *J* = 7.4 Hz), 1.30-1.37 (m, 2H), 1.56-1.63 (m, 2H), 3.78 (s, 3H), 3.85 (t, 2H, *J* = 7.7 Hz), 4.36 (dd, 2H, *J* = 1.7, 1.6 Hz), 5.58 (dt, 1H, *J* = 1.7, 0.9 Hz), 6.35 (dt, 1H, *J* = 1.6, 0.9 Hz), 6.88-6.92 (m, 2H), 7.16-7.19 (m, 2H). ^{13}C

NMR ($CDCl_3$, 176 MHz) δ 13.80, 20.24, 30.42, 41.29, 50.53, 55.53, 114.48, 123.98, 126.84, 132.01, 134.57, 152.74, 158.29, 165.13. ESI-MS $[M+H]^+$ = 289. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65%, H, 6.99%, N, 9.72%. Found: C, 66.49% H, 6.98%, N, 9.63%.

1,3-dicyclohexyl-5-methylidene-1,3-diazinane-2,4-dione (9c) (109 mg, 75%). White solid, mp 82-83 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 5:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2917, 2850, 1702, 1667, 1431, 1412, 1176, 1104, 1052, 966. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.03-1.09 (m, 1H, *H-c*Hex), 1.14-1.21 (m, 1H), 1.26-1.33 (m, 2H), 1.33-1.39 (m, 4H), 1.58-1.66 (m, 4H), 1.68-1.72 (m, 2H), 1.74-1.82 (m, 4H), 2.25-2.30 (m, 2H), 3.85 (dd, 2H, *J* = 1.6, 1.5 Hz), 4.19-4.24 (m, 1H), 4.32-4.36 (m, 1H), 5.49 (dt, 1H, *J* = 1.6, 1.1 Hz), 6.19 (dt, 1H, *J* = 1.5, 1.1 Hz). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 25.53, 25.57, 25.73, 26.58, 29.57, 30.01, 42.39, 54.26, 55.18, 122.91, 133.47, 150.09, 160.66. ESI-MS $[M+H]^+$ = 291. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31%, H, 9.02%, N, 9.65%. Found: C, 70.17%, H, 9.06%, N, 9.57%.

(3-cyclohexyl-1-methyl-5-methylidene-1,3-diazinane-2,4-dione (9d) (88.9 mg, 80%). White solid, mp 78-80 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 4:1). Rf: 0.7 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2922, 2856, 1704, 1661, 1434, 1406, 1204, 1127. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.16-1.23 (m, 1H), 1.28-1.35 (m, 2H), 1.60-1.63 (m, 3H), 1.76-1.80 (m, 2H), 2.27-2.32 (m, 2H), 3.00 (s, 3H), 3.99 (dd, 2H, *J* = 1.8, 1.7 Hz), 4.42-4.47 (m, 1H), 5.52 (dt, 1H, *J* = 1.8, 0.9 Hz), 6.29 (dt, 1H, *J* = 1.7, 0.9 Hz). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 25.54, 26.61, 29.57, 35.57, 49.56, 54.94, 123.71, 132.58, 153.58, 163.57. ESI-MS $[M+H]^+$ = 223. Anal. Calcd for $C_{12}H_{19}N_2O_2$: C, 64.84%, H, 8.16%, N, 12.60%. Found: C, 64.70%, H, 8.19%, N, 12.48%.

1-ethyl-3-phenyl-5-methylidene-1,3-diazinane-2,4-dione (9e) (84.0 mg, 73%). White solid, mp 185-187 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 5:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2970, 1705, 1664, 1492, 1431, 1357, 1215, 1188. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.23 (t, 6H, *J* = 7.2 Hz), 3.53 (q, 2H, *J* = 7.2 Hz), 4.19 (dd, 2H, *J* = 1.8, 1,7 Hz), 5.70 (dt, 1H, *J* = 1.8, 0.8 Hz), 6.43 (dt, 1H, *J* = 1.7, 0.8 Hz), 7.18-7.20 (m, 2H), 7.38 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.43-7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 12.35, 43.23, 47.06, 124.94, 128.38, 128.93, 129.07, 131.98, 135.93, 152.53, 163.31. ESI-MS $[M+H]^+$ = 231. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81%, H, 6.13%, N, 12.17%. Found: C, 67.68%, H, 6.16%, N, 12.24%.

1-cyclohexyl-3-(4-methylphenyl)-5-methylidene-1,3-diazinane-2,4-dione (9f) (107 mg, 72%). White solid, mp 108-110 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 6:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2924, 1702, 1668, 1403, 1352, 1236, 1201. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.11-1.18 (m, 1H), 1.39-1.44 (m, 2H), 1.48-1.54 (m, 2H), 1.70-1.73 (m, 1H), 1.82-1.98 (m, 4H), 2.40 (s, 3H), 4.11 (dd, 2H, *J* = 1.7, 1.6 Hz), 4.28-4.32 (m, 1H), 5.70 (bs, 1H), 6.40 (bs, 1H), 7.09-7.11 (m, 2H), 7.25-7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 21.32, 25.56, 25.75, 29.97, 42.62, 54.81, 124.40, 128.58, 129.75, 132.58, 133.46, 138.13, 152.81, 163.43. ESI-MS $[M+H]^+$ = 299; $[M+Na]^+$ = 321. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46%, H, 7.43%, N, 9.39%. Found: C, 72.60%, H, 7.46%, N, 9.27%.

1-ethyl-3-(4-methylphenyl)-5-methylidene-1,3-diazinane-2,4-dione (9g) (101 mg, 83%). White solid, mp 184-186 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 4:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2972, 1709, 1670, 1477, 1403, 1212, 1188. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.22 (t, 6H, *J* = 7.2 Hz), 2.38 (s, 3H), 3.53 (q, 2H, *J* = 7.2), 4.17 (dd, 2H, *J* = 1.8, 1.7 Hz), 5.68 (dt, 1H, *J* = 1.8, *J* = 0.9 Hz), 6.42 (dt, 1H, *J* = 1.7, 0.8 Hz), 7.06-7.08 (m, 2H), 7.23-7.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 12.32, 21.28, 43.17, 47.01, 124.76, 128.54, 129.76, 132.0, 133.23, 138.17, 152.60, 163.38. ESI-MS $[M+H]^+$ = 245; $[M+Na]^+$ = 267. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83%, H, 6.60%, N, 11.47%. Found: C, 68.65%, H, 6.62%, N,11.36%.

1-methyl-3-(4-methylphenyl)-5-methylidene-1,3-diazinane-2,4-dione (9h) (92.1 mg, 80%). White solid, mp 140-142 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 3:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 2919, 1704, 1671, 1400, 1352, 1218, 1187, 1169, 957. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 2.38 (s, 3H), 3.08 (s, 3H), 4.18 (dd, 2H, *J* = 1.9, 1,8 Hz), 5.69 (dt, 1H, *J* = 1.9, 0.8 Hz), 6.44 (dt, 1H, *J* = 1.8,

0.8 Hz), 7.05-7.07 (m, 2H), 7.23-7.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 21.32, 35.53, 49.48, 125.04, 128.51, 129.85, 131.75, 133.22, 138.28, 153.22, 163.32. ESI-MS $[M+H]^+$ = 231; $[M+Na]^+$ = 253. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81%, H, 6.13%, N, 12.17%. Found: C, 67.60%, H, 6.25%, N, 12.07%.

1-ethyl-3-(4-methoxyphenyl)-5-methylidene-1,3-diazinane-2,4-dione (**9i**) (98.9 mg, 76%). Light brown solid, mp 171-173 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 4:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 2972, 1709, 1666, 1480, 1243, 1217, 1186, 1079, 948. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.22 (t, 3H, *J* = 7.2 Hz), 3.52 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 3H), 4.16 (dd, 2H, *J* = 1.9, 1.8 Hz), 5.68 (dt, 1H, *J* = 1.8, *J* = 0.8 Hz), 6.41 (dt, 1H, *J* = 1.7, 0.8 Hz), 6.93-6.97 (m, 2H), 7.08-7.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 12.32, 43.22, 47.00, 55.51, 114.41, 124.80, 128.51, 129.80, 132.03, 152.70, 159.30, 163.51. ESI-MS $[M+H]^+$ = 261; $[M+Na]^+$ = 283. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60%, H, 6.20%, N, 10.76%. Found: C, 64.46% H, 6.24%, N, 10.76%.

3-(4-methoxyphenyl)-1-methyl-5-methylidene-1,3-diazinane-2,4-dione (9j) (106 mg, 86%). White solid, mp 177-179 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 4:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 3007, 1708, 1674, 1504, 1398, 1352, 1220, 1188, 1035, 959. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 3.08 (s, 3H), 3.81 (s, 3H), 4.17 (dd, 2H, *J* = 1.9, 1.7 Hz), 5.68 (dt, 1H, *J* = 1.9, 0.9 Hz), 6.43 (dt, 1H, *J* = 1.7, 0.9 Hz), 6.94-6.97 (m, 2H), 7.07-7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 35.54, 49.42, 55.52, 114.45, 125.05, 128.48, 129.76, 131.72, 153.30, 159.35, 163.44. ESI-MS $[M+H]^+$ = 247. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40%, H, 5.73%, N, 11.38%. Found: C, 63.62%, H, 5.71%, N, 11.36%.

3-(4-bromophenyl)-1-(4-methoxyphenyl)-5-metyhlidene-1,3-diazinane-2,4-dione (**9k**) **(**184 mg, 95%). White solid, mp 154-156 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 6:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2930, 1709, 1673, 1511, 1400, 1346, 1250, 1207, 1184, 1047, 1012. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 3.80 (s, 3H), 4.51 (dd, 2H, *J* = 1,7, 1,6 Hz), 5.72 (dt, 1H, *J* = 1.7, 0.7 Hz), 6.45 (dt, 1H, *J* = 1.6, 0.7 Hz), 6.91-6.93 (m, 2H), 7.12-7.14 (m, 2H), 7.26-7.29 (m, 2H), 7.55-7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 50.77, 55.53, 114.48, 122.29, 125.57, 126.78, 130.72, 131.64, 132.10, 134.04, 134.69, 152.21, 158.41, 163.14. ESI-MS $[M+H]^+$ = 388. Anal. Calcd for $C_{18}H_{15}BrN_2O_3$: C, 55.83% H, 3.90%, N, 7.23%. Found: C, 55.96%, H, 3.91%, N, 7.21%.

[3-(4-bromophenyl)-1-ethyl-5-methylidene-1,3-diazinane-2,4-dione (**9l**) (127 mg, 82%). White solid, mp 138-140 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 4:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2928, 1704, 1677, 1473, 1399, 1356, 1208, 1185, 1010, 967. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.21 (t, 3H, *J* = 7.2 Hz), 3.51 (q, 2H, *J* = 7.2 Hz), 4.16 (dd, 2H, *J* = 1.8, 1.7 Hz), 5.70 (dt, 1H, *J* 1.8, 0.8 Hz), 6.42 (dt, 1H, *J* = 1.7, 0.8 Hz), 7.05-7.10 (m, 2H), 7.53-7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 12.29, 43.21, 46.92, 122.27, 125.28, 130.71, 131.65, 132.16, 134.92, 152.10, 163.07. ESI-MS $[M+H]^+$ = 310. Anal. Calcd for $C_{13}H_{13}BrN_2O_2$: C, 50.51%, H, 4.24%, N, 9.06%. Found: C, 50.29%, H, 4.35%, N, 9.00%.

3-[4-(dimethylamine)phenyl]-1-methyl-5-methylidene-1,3-diazinane-2,4-dione (**9m)** (114 mg, 88%). White solid, mp 225-227 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:3). Rf: 0.5 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 2884, 1705, 1674, 1521, 1401, 1346, 1222, 1199, 1179, 958. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 2.96 (s, 6H), 3.07 (s, 3H), 4.15 (dd, 2H, *J* = 1.9, *J* = 1.8 Hz), 5.65 (dt, 1H, *J* = 1.9, 0.8 Hz), 6.42 (dt, 1H, *J* = 1.8, 0.8 Hz), 6.73-6.76 (m, 2H), 6.99-7.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 35.53, 40.64, 49.43, 112.66, 124.50, 124.66, 129.02, 131.95, 150.30, 153.58, 163.61. ESI-MS $[M+H]^+$ = 260; $[M+Na]^+$ = 284. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85%, H, 6.61%, N, 16.20%. Found: C, 64.66%, H, 6.68%, N, 16.11%.

1-methyl-3-(pyridin-2-yl)-5-methylidene-1,3-diazinane-2,4-dione (9n) (48.9 mg, 45%). Colourless oil. Chromatography ($CHCl_3$). Rf: 0.4 (UV active, CH_2Cl_2 : AcOEt = 1:2). IR (neat) *v* (cm^{-1}): 2924, 1714, 1674, 1433, 1405, 1354, 1209. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 3.07 (s, 3H), 4.20 (dd, 2H, *J* = 2.3, 2.1 Hz), 5.71 (dt, 1H, *J* = 2.3, 0.8 Hz), 6.45 (dt, 1H, *J* = 2.1, 0.8 Hz), 7.27 (dd, *J* = 7.7, 1.1 Hz), 7.34 (ddd, 1H, *J* = 7.6, 4.9, 1.1 Hz, C*H*$_{Ar}$), 7.82 (ddd, 1H, *J* = 7.7, 7.6, 1.8 Hz), 8.61 (dd, *J* = 4.9, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$,

176 MHz) δ 35.27, 49.54, 123.87, 124.50, 125.53, 131.50, 138.31, 149.61, 152.69, 165.05. ESI-MS $[M+H]^+$ = 218. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82%, H, 5.10%, N, 19.34%. Found: C, 60.85%, H, 5.23%, N, 19.32%.

General procedure for the synthesis of 1,3,6-trisubstituted-5-methylindenedihydrouracils 11a-p

Procedure A (for compounds **11a-c,e-g,c-k,m-o**)

To the solution of 1,3,6-trisubstituted-5-diethoxyphosphoryluracil **10a-c,e-g,c-k,m-o** (0.4 mmol) in dry THF (3 mL) provided with water bath 80% sodium hydride in mineral oil (10.6 mg, 0.44 mmol) was added in argon atmosphere. After 5 min paraformaldehyde (61.3 mg, 2.0 mmol) was added and resulting mixture was stirred for 60 min at rt. Then to the solution water was poured (5 mL) and the mixture was extracted with AcOEt (3 mL) and CH_2Cl_2 (5 mL). Combined organic fractions were washed with brine (5 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting crude product was then purified by column chromatography (eluent CH_2Cl_2 : $CHCl_3$).

Procedure B (for compounds **11d,h,l,p**)

To the solution of 1,3,6-trisubstituted-5-diethoxyphosphoryluracil **10d,h,l,p** (0.4 mmol) in dry THF (2 mL) 36-38% water solution of formaldehyde (0.305 mL, ca. 4.0 mmol) was added at 0 °C. It was followed by addition of Na_2CO_3 (110 mg, 0.8 mmol) dissolved in water (2 mL). The resulting mixture was stirred at 0°C for 30 min and after removal of the ice bath for additional 90 min. After addition of AcOEt (2 mL) the formed layers were separated. The water fraction was then washed with CH_2Cl_2 (3 mL). Organic fractions were combined and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting crude product was then purified by column chromatography (eluent CH_2Cl_2 : $CHCl_3$ or CH_2Cl_2 : AcOEt).

1-Ethyl-3-phenyl-6-methyl-1,3-diazinane-2,4-dione (11a) (79.1 mg, 81%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2973, 1710, 1670, 1493, 1466, 1350, 1216, 1189. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.25 (t, 3H, *J* = 7.2 Hz), 1.47 (d, 3H, *J* = 6.7 Hz), 3.17 (q, 1H, *J* = 7.1 Hz), 3.84 (q, 1H, *J* = 7.2 Hz), 4.23 (q, 1H, *J* = 6.7 Hz), 5.63 (s, 1H), 6.32 (s, 1H), 7.19-7.21 (m, 2H), 7.38 (tt, 1H, *J* = 7.5, 1.3 Hz), 7.43-7.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.49, 21.86, 41.80, 53.85, 123.76, 128.31, 128.85, 129.00, 135.73, 137.84, 151.76, 163.08. ESI-MS $[M+H]^+$ = 245, $[M+Na]^+$ = 267. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83%, H, 6.60%, N, 11.47%. Found: C, 68.78%, H, 6.73%, N,11.56%.

1,6-Diethyl-3-phenyl-1,3-diazinane-2,4-dione (11b) (98.2 mg, 95%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 3:2). IR (neat) *v* (cm^{-1}): 2966, 1710, 1668, 1462, 1433, 1358, 1215, 1188. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.96 (t, 3H, *J* = 7.4 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 1.75-1.82 (m, 1H), 1.82-1.90 (m, 1H), 3.14 (q, 2H, *J* = 7.1 Hz), 3.89 (q, 2H, *J* = 7.2 Hz), 3.87-3.89 (m, 1H), 5.59 (s, 1H), 6.39 (s, 1H), 7.10-7.12 (m, 2H), 7.30 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.35-7.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 9.42, 13.42, 27.65, 42.24, 59.51, 124.85, 128.28, 128.77, 129.98, 135.59, 135.73, 151.94, 163.33. ESI-MS $[M+H]^+$ = 259, $[M+Na]^+$ = 281, $[M+HCOO^-]^-$ = 303. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74%, H, 7.02%, N, 10.84%. Found: C, 69.59 %, H, 7.09%, N, 10.89%.

1-Ethyl-3-phenyl-6-(propan-2-yl)-1,3-diazinane-2,4-dione (11c) (106 mg, 97%). White solid, mp 95-96 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 3:2). IR (neat) *v* (cm^{-1}): 2964, 1709, 1668, 1493, 1463, 1434, 1353, 1215, 1192. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.99 (d, 3H, *J* = 6.9 Hz), 1.01 (d, 3H, *J* = 6.8 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 2.14-2.21 (m, 1H), 3.12 (q, 1H, *J* = 7.1 Hz), 3.86 (d, 1H, *J* = 5.0 Hz), 3.96 (q, 1H,*J* = 7.1 Hz), 5.56 (s, 1H), 6.43 (s, 1H), 7.16-7.19 (m, 2H), 7.37 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.42-7.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.26, 16.95, 18.92, 32.37, 43.19, 63.70, 125.98, 128.26, 128.26, 128.62, 128.96, 133.64, 135.71, 152.06, 163.79. ESI-MS $[M+H]^+$ = 273, $[2M+Na]^+$ = 567. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56%, H, 7.40%, N, 10.29%. Found: C, 70.43%, H, 7.50%, N, 10.30%.

1-Ethyl-3,6-diphenyl-1,3-diazinane-2,4-dione (11d) (91.1 mg, 75%). White solid, mp 147-148 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 2:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 3:2). IR (neat) *v* (cm^{-1}): 2980, 1710, 1671, 1458, 1435, 1350, 1212, 1194. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.21 (t, 3H, *J* = 7.2 Hz), 3.10 (q, 1H, *J* = 7.2 Hz), 3.10 (q, 1H, *J*= 7.1 Hz), 3.98 (q, 1H, *J* = 7,2 Hz), 5.24 (s, 1H), 5.81 (s, 1H), 6.38 (s, 1H), 7.17-7.19 (m, 2H), 7.30-7.33 (m, 2H), 7.35 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.39 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.43-7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.15, 42.56, 61.43, 125.10, 125.83, 128.41, 128.57, 128.77, 129.05, 129.33, 135.62, 136.77, 152.59, 162.71. ESI-MS $[M+H]^+$ = 307, $[2M+Na]^+$ = 635. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49%, H, 5.92%, N, 9.14%. Found: C, 74.37%, H, 5.90%, N, 9.11%.

1-Ethyl-3-(4-methoxyphenyl)-6-methyl-1,3-diazinane-2,4-dione (11e) (84.5 mg, 77%). Light yellow oil, mp 117-118 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 2972, 1709, 1670, 1510, 1464, 1432, 1352, 1254, 1215, 1188. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.24 (t, 3H, *J* = 7.1 Hz), 1.46 (d, 3H, *J* = 6.7 Hz), 3.17 (q, 1H, *J* = 7.1 Hz), 3.83 (q, 1H, *J* = 7.1 Hz), 4.21 (q, 1H, *J* = 6.6 Hz), 5.62 (s, 1H), 6.31 (s, 1H), 6.97-7.00 (m, 2H), 7.12-7.15 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.48, 21.83, 41.81, 53.78, 55.44, 114.35, 123.65, 128.37, 129.75, 137.27, 151.40, 159.08, 163.13. ESI-MS $[M+H]^+$ = 275, $[2M+Na]^+$ = 571. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68%, H, 6.61%, N, 10.21%. Found: C, 65.82% H, 6.55%, N, 10.15%.

1,6-Diethyl-3-(4-methoxyphenyl)-1,3-diazinane-2,4-dione (11f) (111 mg, 96%). Light yellow oil, mp 117-118 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 2:3). IR (neat) *v* (cm^{-1}): 2968, 1709, 1669, 1511, 1461, 1435, 1245, 1214, 1187, 1029. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.94 (t, 3H, *J* = 7.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz), 1.65-1.92 (m, 2H), 3.15 (q, 2H, *J* = 7.1 Hz), 3.84 (s, 3H), 3.90 (q, 2H, *J* = 7.2 Hz), 3.95 (bs, 1H), 5.57 (s, 1H), 6.37 (s, 1H), 6.95-7.00 (m, 2H), 7.09-7.15 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 9.42, 13.42, 27.62, 42.26, 55.44, 59.46, 114.34, 124.75, 128.34, 129.68, 135.63, 152.11, 159.23, 163.56. ESI-MS $[M+H]^+$ = 289, $[2M+Na]^+$ = 599. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65%, H, 6.99%, N, 9.72%. Found: C, 66.41% H, 7.06%, N, 9.69%.

1-Ethyl-3-(4-methoxyphenyl)-6-(propan-2-yl)-1,3-diazinane-2,4-dione (11g) (111 mg, 92%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2966, 1703, 1654, 1510, 1457, 1242, 1218, 1195, 1033, 954. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.96 (d, 3H, *J* = 6,9 Hz), 0.99 (d, 6H, *J* = 6.9 Hz), 1.22 (t, 3H, *J* = 7.1 Hz), 2.15 (oktet, 1H, *J* = 6.9 Hz), 3.11 (q, 1H, *J* = 7,1 Hz), 3.80 (s, 3H), 3.84 (d, 1H, *J* = 5.0 Hz), 3.94 (q, 1H, *J* = 7.1 Hz), 5.54 (s, 1H), 6.41 (s, 1H), 6.96-6.98 (m, 2H), 7.10-7.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.27, 16.94, 18.90, 32.34, 43.20, 55.44, 63.64, 114.31, 125.87, 128.31, 129.52, 133.68, 152.23, 159.21, 164.00. ESI-MS $[M+H]^+$ = 303, $[M+Na]^+$ = 627. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53%, H, 7.33%, N, 9.26%. Found: C, 67.40% H, 7.39%, N, 9.24%.

1-Ethyl-6-phenyl-3-(4-methoxyphenyl)-1,3-diazinane-2,4-dione (11h) (99.6 mg, 74%). White solid, mp 147-148 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 2:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2921, 1710, 1670, 1511, 1463, 1434, 1246, 1215, 1030. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.21 (t, 3H, *J* = 7.1 Hz), 3.10 (q, 1H, *J* = 7.1 Hz), 3.82 (s, 3H), 3.97 (q, 1H, *J* = 7.1 Hz), 5.22 (bs, 1H), 5.79 (s, 1H), 6.37 (s, 1H), 6.94-6.97 (m, 2H), 7.07-7.10 (m, 2H), 7.28-7.31 (m, 2H), 7.35 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.39-7.41 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.28, 42.70, 55.58, 61.52, 55.44, 114.53, 125.08, 125.94, 128.32, 128.65, 129.42, 129.78, 136.94, 138.98, 159.20, 159.45, 162.03. ESI-MS $[M+H]^+$ = 337, $[M+Na]^+$ = 695. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41%, H, 5.99%, N, 8.33%. Found: C, 71.25% H, 6.02%, N, 8.25%.

3-(4-Bromophenyl)-1-ethyl-6-methyl-1,3-diazinane-2,4-dione (11i) (106 mg, 82%). White solid, mp 119-120 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.8 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2973, 1705, 1674, 1463, 1434, 1353, 1249, 1216, 1195, 1011, 970. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.24 (t, 3H, *J* = 7.0 Hz), 1.46 (d, 3H, *J* = 6.7 Hz), 3.17 (q, 1H, *J* = 7.0 Hz), 3.83 (q, 1H, *J* = 7.0 Hz), 4.22 (q, 1H, *J* = 6.7 Hz), 5.64 (s, 1H), 6.32 (s, 1H), 7.05-7.09 (m, 2H), 7.54-7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.46, 21.90, 41.85, 53.81, 122.29, 124.1, 130.64, 132.18, 134.74, 137.56, 151.40, 162.90.

ESI-MS $[M+H]^+$ = 324, $[2M+H]^+$ = 647, $[2M+Na]^+$ = 669. Anal. Calcd for $C_{14}H_{15}BrN_2O_2$: C, 52.03%, H, 4.68%, N, 8.67%. Found: C, 51.91%, H, 4.73%, N, 8.69%.

3-(4-Bromophenyl)-1,6-diethyl-1,3-diazinane-2,4-dione (11j) (131 mg, 97%). Colourless oil. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2926, 1706, 1674, 1461, 1409, 1352, 1214, 1188, 1068, 1010, 968. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.1 Hz), 1.71-1.79 (m, 1H), 1.80-1.88 (m, 1H), 3.14 (q, 2H, *J* = 7.1 Hz), 3.88 (q, 2H, *J* = 7.2 Hz), 3.93-3.96 (m, 1H), 5.60 (s, 1H), 6.39 (s, 1H), 7.05-7.08 (m, 2H), 7.54-7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 9.41, 13.40, 27.67, 42.29, 59.46, 122.25, 125.25, 130.58, 132.15, 134.74, 135.31, 151.58, 163.16. ESI-MS $[M+H]^+$ = 338. Anal. Calcd for $C_{15}H_{17}BrN_2O_2$: C, 53.43%, H, 5.08%, N, 8.31%. Found: C, 53.39%, H, 5.15%, N, 8.19%.

3-(4-Bromophenyl)-1-ethyl-6-(propan-2-yl)-1,3-diazinane-2,4-dione (11k) (138 mg, 98%). White solid, mp 101-102 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 1:1). IR (neat) *v* (cm^{-1}): 2962, 1703, 1663, 1461, 1348, 1246, 1213, 1187, 1012. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 0.96 (d, 3H, *J* = 6.8 Hz), 1.00 (d, 3H, *J* = 6.8 Hz), 1.23 (t, 3H, *J* = 7.1 Hz), 2.16 (oktet, 1H, *J* = 6.7 Hz), 3.11 (q, 1H, *J* = 7.1 Hz), 3.85 (d, 1H, *J* = 5.0 Hz), 3.94 (q, 1H, *J* = 7.1 Hz), 5.57 (s, 1H), 6.43 (s, 1H), 7.04-7.07 (m, 2H), 7.53-7.56 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.24, 16.93, 18.89, 32.35, 44.24, 63.64, 122.22, 126.37, 130.42, 132.13, 133.35, 134.70, 151.71, 163.62. ESI-MS $[M+H]^+$ = 352. Anal. Calcd for $C_{16}H_{19}BrN_2O_2$: C, 54.71%, H, 5.45%, N, 7.98%. Found: C, 54.58%, H, 5.49%, N, 8.07%.

3-(4-Bromophenyl)-1-ethyl-6-phenyl-1,3-diazinane-2,4-dione (11l) (94.0 mg, 61%). White solid, mp 143-144 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 2:1). Rf: 0.9 (UV active, CH_2Cl_2 : AcOEt = 3:2). IR (neat) *v* (cm^{-1}): 2972, 1712, 1672, 1488, 1461, 1433, 1350, 1212. 1187, 1070, 1012. ^{1}H NMR ($CDCl_3$, 700 MHz) 1.21 (t, 3H, *J* = 7.1 Hz), 3.10 (q, 1H, *J* = 7.1 Hz), 3.97 (q, 1H, *J* = 7.1 Hz), 5.24 (bs, 1H), 5.82 (s, 1H), 6.38 (s, 1H), 7.04-7.07 (m, 2H), 7.27-7.30 (m, 2H), 7.34-7.37 (m, 1H), 7.39-7.43 (m, 2H), 7.55-7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 13.21, 42.69, 61.41, 122.47, 125.54, 125.83, 128.82, 129.45, 130.64, 132.29, 134.69, 136.59, 138.73, 152.31, 162.62. ESI-MS $[M+H]^+$ = 386. Anal. Calcd for $C_{19}H_{17}BrN_2O_2$: C, 59.23%, H, 4.45%, N, 7.27%. Found: C, 59.19%, H, 4.48%, N, 7.26%.

3-[4-(Dimethylamine)phenyl]-1,6-dimethyl-1,3-diazinane-2,4-dione (11m) (90.7 mg, 83%). White solid, mp 171-172 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:3). Rf: 0.5 (UV active, CH_2Cl_2 : AcOEt = 1:2). IR (neat) *v* (cm^{-1}): 2972, 1704, 1672, 1608, 1519, 1404, 1345, 1232, 1203, 1183, 1126, 1066. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 1.37 (d, 3H, *J* = 6.7 Hz), 2.96 (s, 6H), 3.07 (s, 3H), 4.16 (q, 1H, *J* = 6.7 Hz), 5.60 (s, 1H), 6.33 (s, 1H), 6.74-7.76 (m, 2H), 6.99-7.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 20.90, 34.06, 40.60, 56.08, 112.66, 123.89, 124.35, 128.99, 137.65, 150.29, 152.75, 163.38. ESI-MS $[M+H]^+$ = 274. Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91%, H, 7.01%, N, 15.37%. Found: C, 65.77%, H, 7.04%, N, 15.41%.

3-[4-(Dimethylamine)phenyl]-6-ethyl-1-methyl-1,3-diazinane-2,4-dione (11n) (100 mg, 87%). White solid, mp 129-130 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:3). Rf: 0.6 (UV active, CH_2Cl_2 : AcOEt = 1:2). IR (neat) *v* (cm^{-1}): 2966, 1707, 1670, 1520, 1408, 1347, 1233, 1201, 1182. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.71-1.79 (m, 1H), 1.82-1.90 (m, 1H) 2.95 (s, 6H), 3.09 (s, 3H), 3.89-3.92 (m, 1H), 5.55 (s, 1H), 6.39 (s, 1H), 6.73-7.76 (m, 2H), 6.98-7.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 9.23, 26.89, 34.61, 40.60, 61.72, 112.64, 124.37, 124.89, 128.92, 135.42, 150.26, 152.90, 163.65. ESI-MS $[M+H]^+$ = 288, $[2M+H]^+$ = 575 Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88%, H, 7.37%, N, 14.62%. Found: C, 66.72%, H, 7.34%, N, 14.70%.

3-[4-(Dimethylamine)phenyl]-1-methyl-6-(propan-2-yl)-1,3-diazinane-2,4-dione (11o) (110 mg, 91%). White solid, mp 135-136 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:3). Rf: 0.6 (UV active, CH_2Cl_2 : AcOEt = 1:2). IR (neat) *v* (cm^{-1}): 2962, 1702, 1666, 1614, 1525, 1448, 1407, 1351, 1236, 1204, 1184, 1070, 965. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.96 (d, 3H, *J* = 6.8 Hz), 1.00 (d, 6H, *J* = 6.8 Hz), 2.20 (oktet, 1H, *J* = 6.6 Hz), 2.96 (s, 6H), 3.12 (s, 3H), 3.81 (d, 1H, *J* = 5.0 Hz), 5.52 (s, 1H), 6.43 (s, 1H), 6.72-6.76 (m, 2H), 6.98-7.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 16.95, 18.78, 31.94, 35.78, 40.61, 66.09, 112.65,

124.37, 125.97, 128.77, 133.48, 150.27, 153.04, 164.13. ESI-MS $[M+H]^+$ = 302, $[2M+H]^+$ = 603. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75%, H, 7.69%, N, 13.94%. Found: C, 67.51%, H, 7.76%, N, 13.90%.

3-[4-(Dimethylamine)phenyl]-6-phenyl-1-methyl-1,3-diazinane-2,4-dione (11p) (91.2 mg, 68%). White solid, mp 181-182 °C. Chromatography (CH_2Cl_2 : $CHCl_3$ 1:2). Rf: 0.7 (UV active, CH_2Cl_2 : AcOEt = 1:2). IR (neat) *v* (cm^{-1}): 2921, 1702, 1668, 1613, 1475, 1406, 1350, 1236, 1204, 1181. ^{1}H NMR ($CDCl_3$, 700 MHz) δ 2.97 (s, 6H), 3.08 (s, 3H), 5.15 (s, 1H), 5.74 (s, 1H), 6.39 (s, 1H), 6.74-6.77 (m, 2H), 7.00-7.04 (m, 2H), 7.27-7.30 (m, 2H), 7.33-7.36 (m, 1H), 7.39-7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 176 MHz) δ 34.86, 40.61, 63.81, 112.67, 124.24, 125.34, 125.86, 128.55, 128.92, 129.36, 136.58, 138.71, 150.35, 153.47, 163.06. ESI-MS $[M+H]^+$ = 336. Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62%, H, 6.31%, N, 12.53%. Found: C, 71.54%, H, 6.35%, N, 12.47%.

General procedure for the synthesis of nonracemic 1,3,6-trisubstituted-5-methylidenediazinane-2,4-diones 11i-l

Procedure A (for compounds **11i-k**)

To the solution of 6-alkyl-3-({bis[(1-phenylethyl)amine]}phosphoryl)-3-(4-bromophenyl)-1-ethyl-1,3-diazinane-2,4-dione **16a-c** (0.5 mmol) in dry THF (2 mL) 80% sodium hydride in mineral oil (16.5 mg, 0.55 mmol) was added in argon atmosphere. After 5 min paraformaldehyde (75.1 mg, 2.5 mmol) was added and resulting mixture was stirred at rt for 4 h. Then to the solution water was poured (3 mL) and the mixture was extracted with CH_2Cl_2 (2 x 5 mL). Combined organic fractions were washed with brine (5 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting crude product was then purified by column chromatography (eluent CH_2Cl_2 : $CHCl_3$ 1:1).

Procedure B (for compounds**11l**)

To the solution of 6-aryl-3-({bis[(1-phenylethyl)amine]}phosphoryl)-3-(4-bromophenyl)-1-ethyl-1,3-diazinane-2,4-dione **16d** (0.5 mmol) in dry THF (2 mL) 36-38% water solution of formaldehyde (0.38 mL, ca. 5.0 mmol) was added at 0 °C. It was followed by addition of Na_2CO_3 (138 mg, 1.0 mmol) dissolved in water (2 mL). The resulting mixture was stirred at 0°C for 30 min and after removal of the ice bath for additional 90 min. After addition of AcOEt (2 mL) the formed layers were separated. The water fraction was then washed with CH_2Cl_2 (3 mL). Organic fractions were combined and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting crude product was then purified by column chromatography (eluent CH_2Cl_2 : $CHCl_3$ 2:1).

(6*R*)-3-(4-Bromophenyl)-1-ethyl-6-methyl-1,3-diazinane-2,4-dione [(*R*)-11i] (107 mg, 83%). White solid, mp 119-121 °C. Er > 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 7.3 min, τ_{minor} = 8.7. $[\alpha]^{25}_D$ = + 26.5 (*c* = 1.0, $CHCl_3$).

(6*S*)-3-(4-Bromophenyl)-1-ethyl-6-methyl-1,3-diazinane-2,4-dione [(*S*)-11i] (112 mg, 87%). White solid, mp 119-121 °C. Er 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 7.3 min, τ_{major} = 8.7. $[\alpha]^{25}_D$ = - 24.0 (*c* = 1.0, $CHCl_3$).

(6*R*)-3-(4-Bromophenyl)-1,6-diethyl-1,3-diazinane-2,4-dione [**(*R*)-11j]** (108 mg, 80%). Colourless oil. Er > 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 6.8 min, τ_{minor} = 8.0. $[\alpha]^{25}_D$ = + 22.8 (*c* = 1.0, $CHCl_3$).

(6*S*)-3-(4-Bromophenyl)-1,6-diethyl-1,3-diazinane-2,4-dione [**(*S*)-11j]** (120 mg, 89%). Colourless oil. Er > 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 6.8 min, τ_{major} = 8.0. $[\alpha]^{25}_D$ = - 21.9 (*c* = 1.0, $CHCl_3$).

(6*R*)-3-(4-Bromophenyl)-1-ethyl-6-(propan-2-yl)-1,3-diazinane-2,4-dione [(*R*)-11k] (112 mg, 80%). White solid, mp 100-102 °C. Er 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column

[hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 6.9 min, τ_{minor} = 8.4. $[\alpha]^{25}_{D}$ = + 31.6 (*c* = 1.0, $CHCl_3$).

(6*S*)-3-(4-Bromophenyl)-1-ethyl-6-(propan-2-yl)-1,3-diazinane-2,4-dione [(*S*)-11k] (111 mg, 79%). White solid, mp 100-102 °C. Er 99 : 1. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{minor} = 6.9 min, τ_{major} = 8.4. $[\alpha]^{25}_{D}$ = - 34.2 (*c* = 1.0, $CHCl_3$).

(6*R*)-3-(4-Bromophenyl)-1-ethyl-6-phenyl-1,3-diazinane-2,4-dione [(*R*)-11l] (78.6 mg, 51%). White solid, mp 143-145 °C. Er > 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 15.5 min, τ_{minor} = 35.2. $[\alpha]^{25}_{D}$ = + 58.5 (*c* = 1.0, $CHCl_3$).

(6*S*)-3-(4-Bromophenyl)-1-ethyl-6-phenyl-1,3-diazinane-2,4-dione [(*S*)-11l] (90.9 mg, 59%). White solid, mp 143-145 °C. Er 99.5:0.5. The er was determined by HPLC using a Chiralpack IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 15.5 min, τ_{major} = 35.2. $[\alpha]^{25}_{D}$ = - 57.3 (*c* = 1.0, $CHCl_3$).

Acknowledgments

Financial support of this work from the National Science Centre of Poland (project DEC-2012/07/B/ST5/02006) is gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

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