The Cohalogenation of 1-*N*-Vinylpyrimidinediones: A New Approach to Nucleoside Analogs

Nathalie Baret,[a] Jean-Pierre Dulcere,*[a] Jean Rodriguez,[a] Jean-Marc Pons,[a] and Robert Faure[b]

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A new approach to the synthesis of nucleoside analogs has been developed, which involves initial chemo- and regioselective cohalogenation of 1-*N*-vinylpyrimidinediones **10a**,**b** using *N*-bromosuccinimide in the presence of variously substituted propargylic alcohols. Radical carbocyclization of the resulting β-bromo propargylic ethers **17–22** then leads to 3-methylenetetrahydrofurans **23–26**. In such cyclizations, different reactivities have been observed for diastereomers **22a**,**b** obtained by cohalogenation with (*R*)-1-benzyloxybut-3-yn-2-ol; although the expected *anti* 3-methylenetetrahydrofurans **27a**,**b** were obtained, the *syn* diastereomers **28a**,**b** were only the minor constituents of a mixture in which bicyclonucleosides **29a**,**b** were the major components. The formation of **29a**,**b** results from a 1,6-hydrogen transfer followed by cyclization, which might be favored by a CH-π interaction in radical intermediate *syn* **II**.

Introduction

The synthesis of nucleoside analogs is of current interest since a large number of these compounds exhibit cytotoxic or antitumor properties.[1] Since modified 2′,3′-deoxyribonucleosides are expected to exhibit clinically important biological activities,[2] particularly as potent inhibitors of the growth of human immunodeficiency virus (HIV), much effort has been directed towards the development of synthetic methods for these derivatives. The dideoxynucleoside analogs are of special interest because they have proven that a simple chemical modification of the sugar moiety can, in a predictable manner, convert a normal substrate for nucleic acid synthesis into a compound with a potent capacity to inhibit, at least in vitro, the replication and cytopathic effect of HTLV-III.[3]

Approaches towards the synthesis of modified nucleosides have been classified into two broad categories:[22]

(i) Divergent approaches that are based on the modification of nucleosides and are therefore limited by the availability of naturally occurring starting materials.[4]

(ii) Convergent approaches that involve the coupling of a nucleoside base with a modified carbohydrate bearing a leaving group at the anomeric center and usually provide α/β equimolecular anomeric mixtures of nucleosides.[5a] Numerous methods have been described for overcoming this drawback associated with the glycosylation, such as intramolecular Vorbrüggen coupling.[5b]

Only a few literature reports relate to the preparation of nucleoside analogs by initial functionalization of 1-*N*-vinylpyrimidinediones. Among these, 1,3-dipolar reactions of vinylnucleoside bases with nitrile oxides[6] and nitrones[7] afford dihydroisoxazoles and 4′-aza nucleoside analogs, respectively. We also recently reported a sequence based on the regio- and chemoselective cohalogenation of 1-*N*-vinylpyrimidinediones, which allowed the preparation of α-aminofuranosides related to nucleosides.[8]

We present here a detailed account of the synthesis of a variety of 2′,3′-deoxyribonucleoside analogs according to this procedure.

Results and Discussion

Although 2′,3′-dideoxy-3′-methylenepyrimidine nucleosides are anticipated to be potential anti-AIDS agents,[9] only a few methodologies for their synthesis have as yet been reported. These involve either oxidation of 5′-*O*-trityl nucleosides, which are subsequently converted into 3′-methylene derivatives,[10] or the coupling of protected 3-methylenexylofuranose derivatives with pyrimidinediones[11] according to Vorbrüggen's procedure.[5b]

In connection with our search for efficient methods for the functionalization of alkenes by cohalogenation,[12] we became interested in the reactivity of enamides as potential precursors of N,O-acetals. Although such transformations have hitherto not been well investigated, we took advantage of the regio- and stereoselectivities reported[13] for the oxidation of enamides to β-bromo α-alkyloxyamides or acetoxyamides in order to obtain bromo propargyloxy derivatives.

We first investigated the use of 1-vinyl-2-pyrrolidone (**1a**) and *N*-vinylphthalimide (**1b**) as model compounds. Treatment of **1a**,**b** with NBS in the presence of propargyl alcohol led to the β-bromo propargyl ethers **2a**,**b**. Tri-*n*-butyltin hy-

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[a] Université dÀiy-Marseille III, Réactivité en Synthèse organique, UMR 6516, Centre de St. Jérôme,
Avenue Escadrille Normandie-Niemen, Boîte D 12,
F-13397 Marseille Cedex 20, France
[b] SM_3B, ESA 6009, Faculté des Sciences et Techniques,
Centre de St. Jérôme,
Avenue Escadrille Normandie-Niemen, Boîte D 12,
F-13397 Marseille Cedex 20, France
Fax: (internat.) + 33-4/91288841
E-mail: jean-pierre.dulcere@reso.u-3mrs.fr

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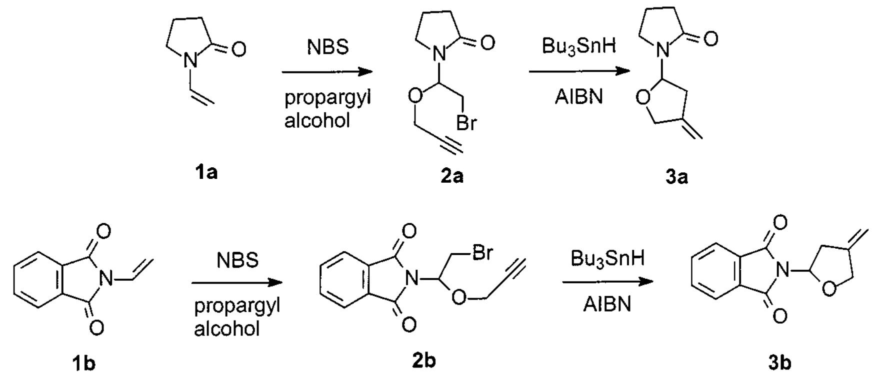


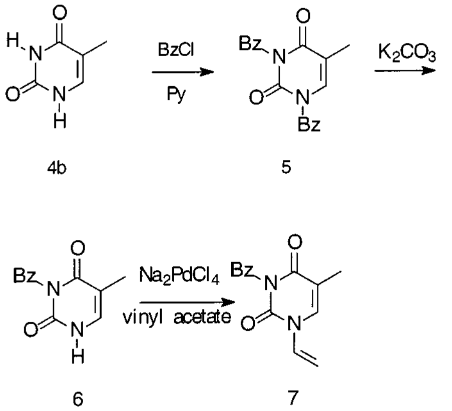
Scheme 1. Functionalization of 1-vinyl-2-pyrrolidine and *N*-vinylphthalimide

dride promoted radical carbocyclization of **2a**,**b** in the 5-*exo* digonal mode[14] afforded 1-(4-methylenetetrahydrofuran-2-yl)pyrrolidone and -phthalimide **3a**,**b** (Scheme 1).

Several procedures have been developed for the preparation of 1-*N*-vinylpyrimidinediones through alkylation of nucleic acid bases.[15] These generally involve conversion of the nucleic acid bases to their *N*-chloroethyl derivatives followed by dehydrochlorination to give the respective *N*-vinyl compounds.[16]

Also of interest are reactions of lactams with enolizable aldehydes, which give the corresponding (*E*)-*N*-alkenyl lactams.[17]

First, we attempted to extend the homogeneous catalytic transvinylation described for cyclic imides and lactams with vinyl acetate[18] to the case of thymine **4b**. We found that good results could be obtained, provided that the substrate was protected as its 3-*N*-benzoyl derivative **6**. Compound **6** was easily obtained according to a reported two-step procedure[19] (Scheme 2).

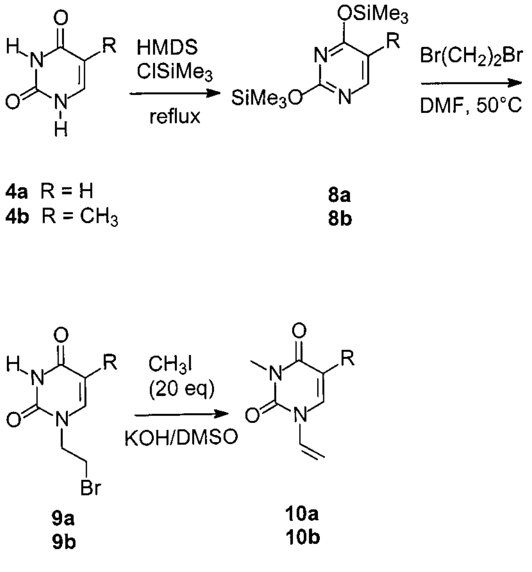


Scheme 2. Preparation of 3-*N*-benzoyl-1-*N*-vinylthymine

Indeed, difficulties associated with the direct exchange of the acetyl group of vinyl acetate with uracil or thymine have recently been reported,[6a] which are clearly attributable to the presence of four nucleophilic centers.

Selective 1-*N*-alkylation of pyrimidine bases according to a radical $S_{RN}1$ mechanism has also been reported as a route to 1-*N*-alkylated cytosine, which allows access to 1-*N*-vinylcytosine through treatment with base.[20] However, uracil **4a** and thymine **4b** were found not to be amenable to similar transformations.

The most widely utilized procedure for the preparation of 1-*N*-substituted nucleic bases is the Vorbrüggen reaction,[5b] which involves the conversion of pyrimidinedione bases to their bis(trimethylsilyl) ether derivatives by treatment with hexamethyldisilazane and chlorotrimethylsilane. The bis(trimethylsilyl) derivative is then alkylated[21] by treatment with 3 equiv. of the appropriate dibromoalkane in DMF to afford the corresponding bromoalkyl pyrimidine derivative. According to this two-step procedure, uracil and thymine were converted to their bis(trimethylsilyl) derivatives **8a** and **8b**, respectively, and these were then alkylated using excess 1,2-dibromoethane in DMF to afford 1-(2-bromoethyl)uracil **9a** and -thymine **9b** (Scheme 3).

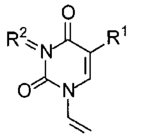
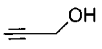
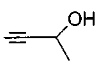
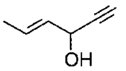
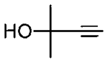
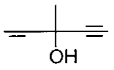
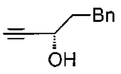
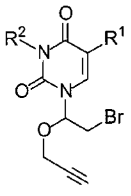
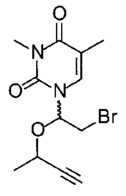
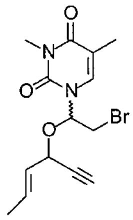
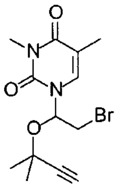
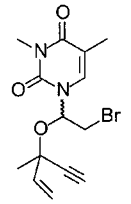
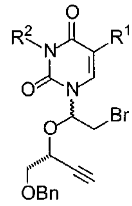


Scheme 3. Preparation of 3-methyl-1-vinylpyrimidinediones

For the subsequent dehydrobromination step, various reaction conditions tested proved unsuccessful (DBU, KOH/H_2O, KOH/DMSO). Although the use of *t*BuOK/DMSO led to a crude reaction mixture in which vinylic protons could be detected by ^{1}H-NMR spectroscopy, the low solubility of the products during work-up prompted us to adopt a novel one-pot methylation–dehydrobromination procedure to circumvent this drawback. To this end, 1-bromoethylpyrimidinediones **9a**,**b** were reacted with excess CH_3I/KOH in DMSO, which resulted in both methylation at N-3 and dehydrobromination to afford 3-methyl-1-vinylpyrimidinediones **10a**,**b** (Scheme 3).

Functionalization of vinylpyrimidinediones **7** and **10a**,**b** by addition of propargylic alcohols **11–16** in the presence of NBS at –40 °C proved to be regio- and chemoselective with respect to the exocyclic double bond. Only the β-bromo propargyl ethers **17–22** were isolated in moderate to good yields (Table 1).

Table 1. Preparation of β-propargyl ethers **17–22**

1-*N*-vinyl-pyrimidine-dione	 **10a** R^1 = H, R^2 = CH_3 **10b** R^1 = R^2 = CH_3 **7** R^1 = CH_3, R^2 = Bz	**10b**	**10b**	**10b**	**10b**	**10a** **10b** **7**
alkynol	 **11**	 **12**	 **13**	 **14**	 **15**	 **16**
product	 **17a 17b 17c**	 **18**	 **19**	 **20**	 **21**	 **22a 22b 22c**
yield	61 98 95	55	76	46	33	61 95 95

Interestingly, even in the presence of 3 equiv. of NBS, the C5–C6 unsaturation proved to be unreactive, even though functionalization of this double bond in pyrimidinediones proceeds quantitatively at room temperature to afford 5-bromo-6-propynyloxy adducts.[22]

The use of secondary alcohols **12** and **13** allowed the formation of N,O-acetals, which were isolated as mixtures of diastereomers. Compared to the cohalogenation with propargyl alcohol **11**, longer reaction times were required with the secondary and tertiary alcohols **12–15** and lower yields were achieved.

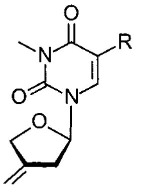
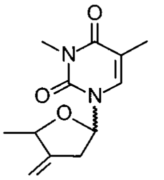
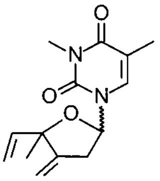
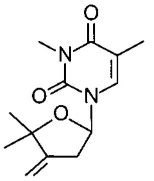
With the aim of developing a novel access to deoxyribose derivatives, we performed cohalogenations of 3-methyl-1-vinyluracil and thymine **10a**,**b** and 3-benzoyl-1-vinylthymine **7** using NBS in the presence of the secondary acetylenic alcohol (*R*)-1-benzyloxybut-3-yn-2-ol **16**,[23] in which the future 5′ primary hydroxyl group present in the nucleoside series is protected as a benzyl ether. This afforded an inseparable diastereomeric mixture of N,O-acetals **22** in a 55:45 ratio.

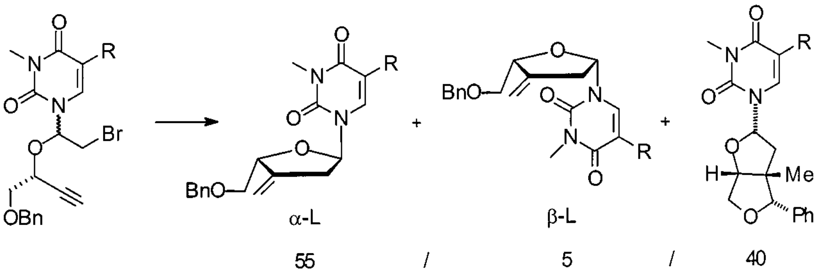
Radical carbocyclizations of the β-bromo alkynyl ethers **17–22** were carried out according to the standard procedure [addition of 1.2 equiv. Bu_3SnH, AIBN (cat.) to a 0.4 M solution in benzene; reflux] to afford selectively[24] methylenetetrahydrofurans **23–26**; compounds **24** and **25** were isolated as 1.5:1 and 1.2:1 diastereomeric mixtures, respectively. However, attempted carbocyclizations of unsaturated ethers **17c**, **21**, and **22c** did not give any cycloadducts. Surprisingly, under the reaction conditions, **17c** and **22c** underwent a β-elimination process to give 3-*N*-benzoyl-1-*N*-vinylthymine (**7**) as the sole product, while **21** underwent polycondensation (Table 2).

Radical carbocyclization of the diastereomeric mixture of N,O-acetals **22** was accomplished under different reaction conditions. Refluxing a 0.05 M benzene solution of **22** containing Bu_3SnH (1.2 equiv.) and catalytic amounts of AIBN for 6 h resulted in the formation of an inseparable 11:1 diastereomeric mixture of the expected 3-methylenetetrahydrofurans L-α-**27** and L-β-**28** (60%), together with 40% of an unexpected bicyclonucleoside **29** containing four stereogenic centers (Scheme 4).

The ^1H- and ^{13}C-NMR chemical shifts, and consequently the molecular frameworks of compounds **27**, **28**, and **29**, were deduced from the concerted application of gradient-enhanced (ge) homonuclear and both direct and long-range ^1H-detected heteronuclear chemical shift correlation experiments. The proton network could be established from the

Table 2. Formation of methylenetetrahydrofurans **23–26**

β-propargyl ether	**17a**	**17b**	**17c**	**18**	**19**	**20**	**21**	**22c**
product							Polycon- densation	
	R = H **23a**	R = CH_3 **23b**	**7**	**24**	**25**	**26**		**7**
Yield %	45	50	30	92	28	90	-	65



22a **22b** → **27a** **27b** + **28a** **28b** + **29a** **29b**

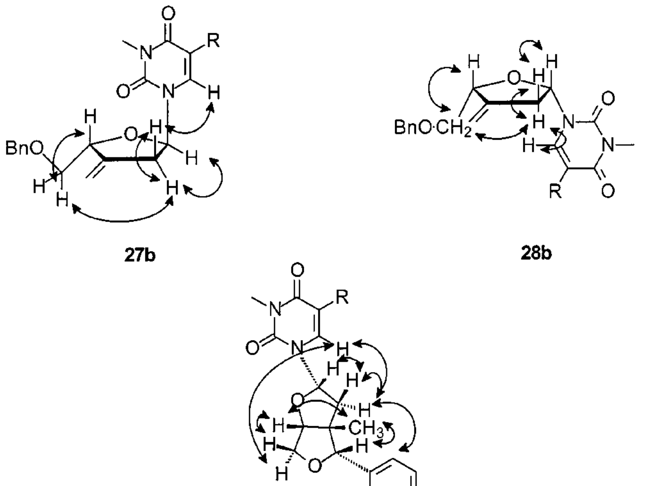
a, R = H
b, R = CH_3

Scheme 4. Radical carbocyclization of N,O-acetals **22**

ge-COSY diagram.[25] One-bond proton-carbon chemical shift correlations were delineated using the ge-HM_2C technique.[26] Finally, the various $(CH)_n$ groups were assigned and assembled from analysis of long-range correlation responses over two or three bonds (^2J and ^3J couplings) by means of the ge-HMBC sequence.[27] The stereochemistry of compounds **27**, **28**, and **29** was unequivocally established on the basis of NOE cross-peaks observed in a phase-sensitive NOESY experiment,[28] as shown in Figure 1.

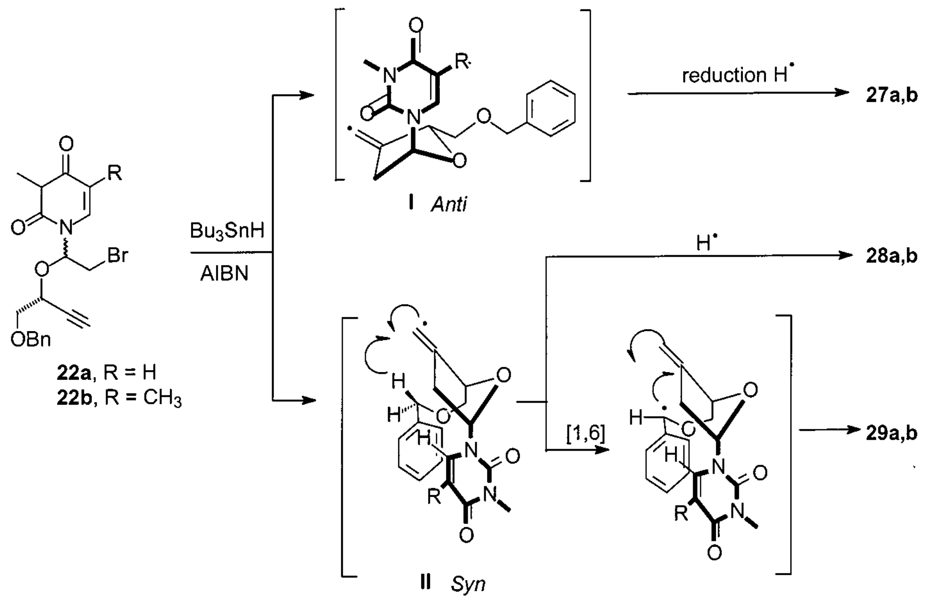
The diastereomeric ratio of the mixture of 3-methylenetetrahydrofurans **27** and **28** indicates that the two diastereomers of **22** are formed according to two different pathways. Indeed, the major isomer gives rise to the *anti* radical intermediate **I** through a direct 5-*exo*-dig ring-closure, which then undergoes proton abstraction to form L-α-**27**. In marked contrast, the minor isomer of **22** is transformed according to two distinct pathways: 5-*exo*-dig ring-closure furnishes the *syn* vinyl radical intermediate **II**, which generates a small amount of the *syn* methylenetetrahydrofuran L-β-**28** through proton abstraction; the main transformation, however, is a 1,6-hydrogen atom transfer followed by 5-*exo*-trig ring closure, leading to the corresponding bicyclonucleoside **29** (Scheme 5).

In order to rationalize this unexpected bis-cyclization, we decided to carry out semi-empirical AM1 calculations in order to obtain information on both the energies (heats of formation) and preferred geometries (conformations) of the relevant products. Thus, calculations (AM1/RHF)[29] were performed on methylenetetrahydrofuran **27b**, bicyclonucle-



27b **28b** **29b**

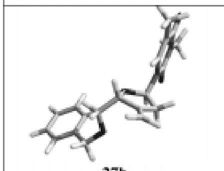
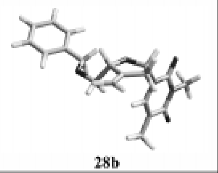
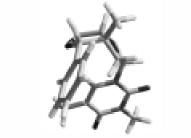
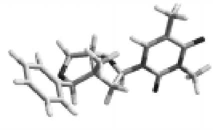
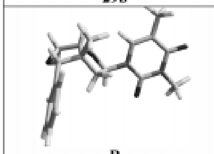
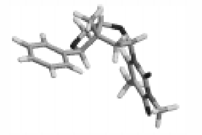
Figure 1. Selected through-space interaction pathways deduced from phase-sensitive NOESY spectra of **27**, **28**, and **29**



Scheme 5. Evolution of *anti* radical **II** and *syn* radical **II**

oside **29b**, and its monocyclic isomer **28b**, as well as on the non-observed diastereomeric bicyclonucleosides **A**, **B**, and **C** (Table 3).

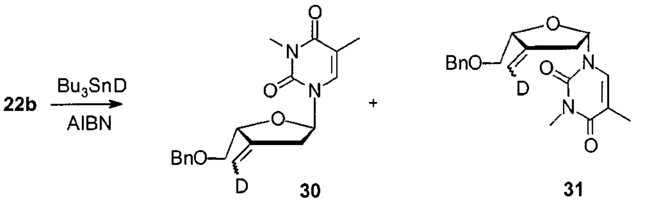
Table 3. Semi-empirical AM1 calculations on methylenetetrahydrofurans and bicyclonucleosides

diastereomers	ΔHf (kcal/mol)	diastereomers	ΔHf (kcal/mol)
 27b	-84.0	 28b	-85.8
 29b	-101.0	 A	-99.6
 B	-99.6	 C	-98.9

The calculations indicate that the bicyclic adduct **29b** is more stable than monocyclic species **27b** and **28b**, as would be the diastereomeric adducts **A**, **B**, and **C**, which are not detected.

Since the energies of **29b**, **A**, **B**, and **C** are very close, the exclusive formation of **29b** probably arises from a significant difference in the activation energies associated with the formation of these species. The relative stabilization of the transition state leading to **29b** could result from an interaction between the aromatic ring of the benzyl ether and the pyrimidinedione nucleus, *which can only occur in this particular case.* The calculated structure of the most stable conformer of **29b** suggests that a CH-π interaction[30a] is involved rather than a π-stacking one.[31] Indeed, we were unable to find a stable conformation of **29b** involving a π-stacking interaction.

This CH-π interaction in radical L-β-*syn* **II** might provide a conformational preference allowing the occurrence of the diastereoselective 1,6-hydrogen transfer in the *syn* radical intermediate **I**, thereby accounting for both the selective formation of bicyclic adduct **29** as well as the total diastereoselectivity observed in forming the four stereogenic centers (Scheme 6).



Scheme 6. Bu_3SnD (2 equiv.) mediated carbocyclization of **22b**

The 1,6-hydrogen transfer is not sterically allowed in the *anti* radical **II**, which is thus further reduced to give the expected 3-methylenetetrahydrofurans **27**. Interestingly, the influence of such CH-π interactions on the diastereoselectivities of radical carbocyclizations have only scarcely been mentioned in the literature.[30b]

This intramolecular hydrogen atom transfer did not occur when an excess of the stannane (2 equiv.) was added in one portion to a refluxing solution of **22b** in benzene. Under the same reaction conditions, addition of Bu_3SnD resulted in the exclusive formation of 3-methylenetetrahydrofurans **30** and **31** deuterated at the vinylic position (Scheme 6). This indicates that the 1,6-hydrogen atom transfer is dependent on the reaction conditions, in marked contrast to a recently reported intramolecular hydrogen atom transfer mediated carbocyclization.[32]

Moreover, the 1,6-hydrogen atom transfer is similarly prevented in the radical cyclization of **22b** promoted by

SmI_2 since the alkenyl radical **II** formed in this case can very easily be reduced to 3-methylenetetrahydrofurans **28b** and **29b** under the reaction conditions.[33]

Conclusion

Since numerous approaches for the synthesis of optically active acetylenic alcohols are available,[23] the strategy described herein should provide an efficient enantioselective access to modified nucleosides **4** and bicyclonucleosides **6**. Related bicyclonucleoside structures have been mentioned only recently in the literature.[34] Although the obtained adducts have yet to be fully characterized and other separation techniques are still being investigated in this context, the work reported here represents a new and straightforward route to the synthesis of modified nucleosides.

Experimental Section

General Remarks: ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AC 200 or AMX 400 spectrometers. $CDCl_3$ was used as solvent, unless otherwise specified. Chemical shifts are given in ppm (δ) referenced to residual, non-deuterated solvent ($CHCl_3$, δ = 7.24). – IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer; absorbances are given in cm^{-1}; liquids were examined as films, solids were dissolved in $CHCl_3$. – Melting points (uncorrected): Büchi apparatus. – Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl (dark blue-purple color) under N_2 atmosphere. – Flash column chromatography was performed on silica gel 60 (Merck 230–400 mesh) and TLC on precoated silica gel sil G/UV$_{254}$ plates (Macherey Nagel).

Preparation of 1-*N*-Vinylphthalimide (1b): To a stirred solution of phthalimide (0.594 g, 4 mmol) in vinyl acetate (10 mL, 26.8 equiv.) under argon was added Na_2PdCl_4 (11.2 mg) and the mixture was heated under reflux for 8 h. Activated charcoal (15 mg) was then added and the mixture was stirred for 10 min. It was then diluted with diethyl ether (20 mL), the solids were removed by filtration, and the filtrate was concentrated to dryness under high vacuum. The crude product was extracted with diethyl ether and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized to afford 662 mg (95%) of **7** in the form of yellow crystals; m.p. 174–175 °C. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.02 (d, *J* = 9.8 Hz, 1 H), 6.05 (d, *J* = 16.4 Hz, 1 H), 6.81 (dd, *J* = 16.4 and 9.8 Hz, 1 H), 7.53–7.87 (m, 4 H). – $C_{10}H_7NO_2$ (173.17): calcd. C 69.36, H 4.07, N 8.09; found C 69.25, H 4.15, N 8.13.

Preparation of β-Bromopropargyl Ethers: A solution of the appropriate alkene (1.0 mmol) in propargyl alcohol (1.1 mL, 19 equiv.) was placed in a 10 mL flask under N_2. After cooling to –30 °C, NBS (214 mg, 1.2 equiv.) was added in five portions over a period of 15 min. The reaction mixture was stirred for 2 h at room temperature and then poured into CH_2Cl_2. The resulting solution was washed with aq. sodium bisulfite solution and water, and dried over $MgSO_4$. The solvent was then evaporated and the residue was chromatographed on silica gel.

1-[2-Bromo-1-(prop-2-ynyloxy)ethyl]pyrrolidin-2-one (2a): Yield: 241 mg (98%). – IR: ṽ = 3282, 2973, 2117, 1697, 1421, 1279, 1178, 1058 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.05 (m, 2 H), 2.39 (m, 2 H), 2.43 (t, *J* = 2.4 Hz, 1 H), 3.32 (dd, *J* = 10.8 and 8.2 Hz, 1 H), 3.40 (m, 2 H), 3.52 (dd, *J* = 10.8 and 5.4 Hz, 1 H), 4.09 (dd, *J* = 15.8 and 2.4 Hz, 1 H), 4.19 (dd, *J* = 15.8 and 2.4 Hz, 1 H), 5.57 (dd, *J* = 8.2 and 5.4 Hz, 1 H). – ^{13}C NMR (50.3 MHz): δ = 17.7, 29.2, 30.8, 41.0, 56.1, 74.5, 78.8, 79.9, 176.2. – $C_9H_{12}BrNO_2$ (246.10): calcd. C 43.92, H 4.91, N 5.69; found C 43.80, H 5.09, N 5.61.

1-[2-Bromo-1-(prop-2-ynyloxy)ethyl]phthalimide (2b): Yield: 268 mg (87%). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.31 (t, *J* = 2.3 Hz, 1 H), 3.85 (dd, *J* = 10.5 and 5.7 Hz, 1 H), 4.16 (dd, *J* = 10.5 and 8.6 Hz, 1 H), 4.24 (d, *J* = 2.3 Hz, 2 H), 5.72 (dd, *J* = 8.5 and 5.6 Hz, 1 H), 7.75 (m, 2 H), 7.83 (m, 2 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.3, 57.2, 75.4, 78.2, 80.1, 123.7, 131.3, 134.5, 167.3. – $C_{13}H_{10}BrNO_3$ (308.13): calcd. C 50.67, H 3.27, N 4.55; found C 50.59, H 3.42, N 4.50.

1-[2-Bromo-1-(prop-2-ynyloxy)ethyl]-3-methyl-1*H*-pyrimidine-2,4-dione (17a): Yield: 175 mg (61%). – IR: ṽ = 3285, 2968, 2119, 1705, 1669, 1459, 1414, 1105 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.47 (m, 1 H), 3.19 (s, 1 H), 3.44 (dd, *J* = 11.1 and 5.3 Hz, 1 H), 3.51 (dd, *J* = 11.1 and 5.3 Hz, 1 H), 4.14 (m, 2 H), 5.72 (d, *J* = 8.1 Hz, 1 H), 5.97 (t, *J* = 5.3 Hz, 1 H), 7.27 (d, *J* = 8.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.6, 31.3, 57.3, 76.6, 77.0, 82.9, 102.0, 136.6, 151.2, 162.4. – $C_{10}H_{11}BrN_2O_3$ (287.11): calcd. C 41.83, H 3.86, N 9.76; found C 41.74, H 4.02, N 9.72.

1-[2-Bromo-1-(prop-2-ynyloxy)ethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (17b): Yield: 295 mg (98%). – IR: ṽ = 3100, 2962, 2120, 1707, 1673, 1644, 1103 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.96 (d, *J* = 1.1 Hz, 3 H), 2.49 (t, *J* = 2.4 Hz, 1 H), 3.34 (s, 3 H), 3.49 (dd, *J* = 11.2 and 5.7 Hz, 1 H), 3.58 (dd, *J* = 11.2 and 5.7 Hz, 1 H), 4.23 (m, 2 H), 6.12 (t, *J* = 5.6 Hz, 1 H), 7.13 (q, *J* = 1.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.4, 28.1, 28.4, 31.2, 57.4, 76.5, 77.3, 82.9, 110.8, 132.2, 151.5, 163.4. – $C_{11}H_{13}BrN_2O_3$ (301.14): calcd. C 43.87, H 4.35, N 9.30; found C 43.78, H 4.42, N 9.24.

3-Benzoyl-1-[2-bromo-1-(prop-2-ynyloxy)ethyl]-5-methyl-1*H*-pyrimidine-2,4-dione (17c): Yield: 372 mg (95%). – IR: ṽ = 3310, 3020, 2120, 1753, 1704, 1097, 776, 742 cm^{-1}. – ^{1}H NMR: δ = 1.98 (s, 3 H), 2.54 (t, *J* = 2.3 Hz, 1 H), 3.58 (m, 2 H), 4.28 (m, 2 H), 6.05 (t, *J* = 5.8 Hz, 1 H), 7.33 (s, 1 H), 7.47 (s, 2 H), 7.63 (m, 1 H), 7.91 (m, 2 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.7, 31.1, 57.8, 76.8, 77.3, 82.7, 111.8, 129.2 (2 CH), 130.4 (2 CH), 131.5, 134.1, 135.1, 149.8, 162.5, 168.5. – $C_{17}H_{15}BrN_2O_4$ (391.22): calcd. C 52.19, H 3.86, N 7.16; found C 52.09, H 4.04, N 7.12.

1-[2-Bromo-1-(1-methylprop-2-ynyloxy)ethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (18): Yield: 173 mg (55%). – IR: ṽ = 3310, 3018, 2120, 1750, 1700, 1100 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.48 and 1.46 (d, *J* = 6.6 Hz, 3 H), 1.95 (s, 3 H), 2.34 and 2.54 (d, *J* = 1.9 Hz, 1 H), 3.33 (s, 6 H), 3.37–3.57 (m, 2 H), 4.23 and 4.38 (qd, *J* = 6.6 and 1.9 Hz, 1 H), 6.06 and 6.25 (t, *J* = 5.9 and 5.5 Hz, 1 H), 7.19 and 7.12 (q, *J* = 1.2 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.4 and 15.2, 21.6 and 21.9, 27.9, 31.4 and 31.6, 65.7 and 66.8, 74.2 and 75.3, 81.2 and 83.4, 110.0 and 110.6, 132.0 and 132.9, 151.3, 163.6. – $C_{12}H_{15}BrN_2O_3$ (315.16): calcd. C 45.73, H 4.80, N 8.89; found C 45.82, H 4.76, N 8.81.

1-[2-Bromo-1-(1-ethynylbut-2-ynyloxy)ethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (19): Yield: 259 mg (76%). – IR: ṽ = 3292, 2963, 2117, 1701, 1668, 1639, 1100, 1045 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.73 (d, *J* = 6.5 Hz, 3 H), 1.95 and 1.96 (s, 3 H), 2.53 and 2.62 (d, *J* = 2.0 Hz, 1 H), 3.34 (s, 3 H), 3.41 and 3.57 (m, 2 H), 4.62 and 4.66 (m, 1 H), 5.45 and 5.53 (m, 1 H), 5.97 and 6.02 (m, 1 H), 6.07 and 6.22 (dd, *J* = 5.6 Hz, 1 H), 7.15 and 7.19 (m, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.5, 17.6, 28.1, 31.5 and 31.8, 69.2 and 70.3, 76.2 and 77.0, 79.0 and 79.6, 80.9 and 81.6, 108.6 and 110.5, 125.9 (2 CH), 132.5 and 132.6, 132.8 and 133.3, 151.4, 163.5. – $C_{14}H_{17}BrN_2O_3$ (341.20): calcd. C 49.28, H 5.02, N 8.21; found C 49.20, H 5.15, N 8.16.

1-[2-Bromo-1-(1,1-dimethylprop-2-ynyloxy)ethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (20): Yield: 151 mg (46%). – IR: ṽ = 3301, 3018, 2112, 1701, 1670, 1638, 1100 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 1.58 (s, 3 H), 1.98 (s, 3 H), 2.46 (s, 1 H), 3.35 (s, 3 H), 3.50 (m, 2 H), 6.31 (t, *J* = 4.5 Hz, 1 H), 7.23 (s, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.4, 28.0, 28.8, 29.2, 32.7, 72.6, 73.8, 79.4, 83.9, 110.0, 132.9, 151.0, 163.6. – $C_{13}H_{17}BrN_2O_3$ (329.19): calcd. C 47.43, H 5.21, N 8.51; found C 47.35, H 5.24, N 8.49.

1-[2-Bromo-1-(1-ethynyl-1-methylallyloxy)ethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (21): Yield: 113 mg (33%). – IR: ṽ = 3302, 3018, 2110, 1700, 1639, 1046, 928 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.56 and 1.59 (s, 3 H), 1.94 and 1.96 (d, *J* = 1.1 Hz, 3 H), 2.45 and 2.71 (s, 1 H), 3.18 and 3.31 (s, 3 H), 3.42 and 3.51 (m, 2 H), 5.06 (m, 2 H), 5.87 (m, 1 H), 6.13 and 6.19 (t, *J* = 5.5 Hz, 1 H), 7.16 and 7.23 (q, *J* = 1.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.4 and 13.6, 27.9, 32.6 and 32.8, 75.6, 76.6, 79.5, 80.7, 109.5 and 109.8, 117.9 and 120.0, 133.2 and 133.4, 137.2 and 137.4, 150.8 and 150.9, 163.7 and 163.8. – $C_{14}H_{17}BrN_2O_3$ (341.20): calcd. C 49.28, H 5.02, N 8.21; found 49.20, H 5.15, N 8.25.

1-[1-(1-Benzyloxymethylprop-2-ynyloxy)-2-bromoethyl]-3-methyl-1*H*-pyrimidine-2,4-dione (22a): Yield: 248 mg (61%). – IR: ṽ = 3293, 2919, 2860, 2119, 1708, 1668, 1196, 910 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 2.55 and 2.48 (d, *J* = 2.1 Hz, 1 H), 3.35 and 3.36 (s, 3 H), 3.40–3.78 (m, 4 H), 4.28 (m, 1 H), 4.54 (m, 2 H), 5.64 and 5.79 (d, *J* = 8.1 Hz, 1 H), 6.16 (m, 1 H), 7.31 (m, 5 H), 7.39 and 7.42 (d, *J* = 8.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.8 and 28.3, 32.1 and 32.2, 68.3 and 68.7, 70.5 and 70.8, 71.7 and 72.0, 73.6 (2 CH_2), 77.1 and 77.5, 82.4 and 81.8, 101.9 and 104.7, 127.7 and 127.8, 127.9 and 128.1, 128.6 and 128.7, 136.4 and 137.0, 137.2 and 137.4, 150.6 and 151.4, 161.8 and 162.7. – $C_{18}H_{19}BrN_2O_4$ (407.26): calcd. C 51.92, H 4.36, N 7.12; found C 51.80, H 4.52, N 7.15.

1-[1-(1-Benzyloxymethylprop-2-ynyloxy)-2-bromoethyl]-3,5-dimethyl-1*H*-pyrimidine-2,4-dione (22b): Yield: 400 mg (95%). – IR: ṽ = 3301, 3017, 2924, 2121, 1696, 1667, 1640, 1100 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.92 and 1.93 (s, 3 H), 2.41 and 2.55 (d, *J* = 2.2 Hz, 1 H), 3.32 and 3.33 (s, 3 H), 3.40–3.78 (m, 4 H), 4.29 (ddd, *J* = 8.3, 3.2 and 2.2 Hz, 1 H), 4.50 (ddd, *J* = 6.3, 5.1 and 2.2 Hz, 1 H), 4.53 and 4.56 (d, *J* = 3.9 Hz and s, 1 H), 6.17 and 6.19 (t, *J* = 5.6 Hz, 1 H), 7.22 (s, 1 H), 7.31 (m, 5 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.1 and 13.3, 28.0, 31.4 and 31.9, 61.6 (2 CH), 68.2 and 70.3, 71.9 and 72.2, 73.4 and 73.6, 76.2 and 76.8, 81.7 and 84.0, 110.4 (2 C), 127.7 and 127.9, 128.0 and 128.1, 128.6, 132.6 and 133.0, 136.7 and 137.5, 150.5 and 151.6, 163.8 and 166.2. – $C_{19}H_{21}BrN_2O_4$ (421.29): calcd. C 53.09, H 4.70, N 6.88; found C 52.97, H 4.72, N 6.79.

3-Benzoyl-1-[1-(benzyloxymethylprop-2-ynyloxy)-2-bromoethyl]-5-methyl-1*H*-pyrimidine-2,4-dione (22c): Yield: 486 mg (95%). – IR: ṽ = 3297, 3033, 2120, 1749, 1700, 1664, 1599, 1104 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of diastereomers): δ = 1.74 and 1.94 (s, 3 H), 3.60–3.71 (m, 2 H), 4.04 (d, *J* = 7.0 Hz, 2 H), 4.41 (m, 1 H), 4.60 (m, 2 H), 6.12 (dd, *J* = 5.9 and 5.5 Hz, 1 H), 6.71 (dd, *J* = 8.9 and 7.1 Hz), 7.16 (s, 1 H), 7.32 (m, 5 H), 7.48–7.91 (m, 5 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.5 and 12.7, 31.7 and 31.9, 68.4 and 70.5, 71.7 and 72.0, 73.6 and 73.7, 76.8 and 77.3, 81.3 and 83.3, 127.7 (2 CH) and 127.8 (2 CH), 128.2 and 128.4, 128.7 (2 CH) and 128.8 (2 CH), 129.3 (2 CH) and 129.4 (2 CH), 130.5 (2 CH) and 130.6 (2 CH), 131.2 and 131.5, 134.5 and 134.8, 135.2 and 135.4, 137.4 and 137.5, 148.7 and 149.8, 161.9 and 162.7, 167.8 and 168.7. – $C_{25}H_{23}BrN_2O_5$ (511.37): calcd. C 57.96, H 4.26, N 5.63; found C 57.90, H 4.35, N 5.58.

General Procedure for the Preparation of 1-(2-Bromoethyl)uracil (9a) and 1-(2-Bromoethyl)thymine (9b): To a solution of the pyrimidinedione **4** (17.8 mmol) [uracil **4a** (2.0 g) or thymine **4b** (2.24 g)] in hexamethyldisilazane (11.4 mL, 54 mmol, 3 equiv.) under argon was added a catalytic amount of $ClSiMe_3$ (1.08 mL, 0.5 equiv.) and the mixture was refluxed for 21 h. Excess HMDS was then removed under reduced pressure to afford crude *O*-silylated uracil or thymine. The crude material was taken up in DMF (10 mL), 1,2-dibromoethane (4.6 mL, 3 equiv.) was added, and the mixture was stirred at 80 °C for 24 h. Water (150 mL) was then added and, after stirring for 10 min., the mixture was filtered and the aqueous filtrate was extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crystallization of the residue from absolute EtOH gave white crystals of **9a** and **9b**.

1-(2-Bromoethyl)-1*H*-pyrimidine-2,4-dione (9a): Yield: 1.21 g (31%); m.p. 142–144 °C. – IR ($CHCl_3$): ṽ = 3390, 2978, 2895, 1692 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.64 (t, *J* = 5.69 Hz, 2 H), 4.10 (t, *J* = 5.69 Hz, 2 H), 5.71 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 1 H), 9.55 (s, 1 H, N^3–H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 29.7, 51.0, 102.0, 145.3, 150.9, 164.1. – $C_6H_7BrN_2O_2$ (219.03): calcd. C 32.90, H 3.22, N 12.79; found C 32.81, H 3.29, N 12.85.

1-(2-Bromoethyl)-5-methyl-1*H*-pyrimidine-2,4-dione (9b): Yield: 2.49 g (60%); m.p. 184–185 °C. – IR ($CHCl_3$): ṽ = 3389, 2980, 1691, 1106 cm^{-1}. – ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.92 (s, 3 H), 3.68 (t, *J* = 6.28 Hz, 2 H), 4.01 (t, *J* = 6.28 Hz, 2 H), 7.55 (s, 1 H), 11.34 (s, 1 H, N^3–H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.2, 30.9, 48.8, 108.5, 141.7, 151.0, 164.5. – $C_7H_9BrN_2O_2$ (233.06): calcd. C 36.07, H 3.89, N 12.02; found C 35.92, H 3.92, N 12.12.

General Procedure for the Preparation of 3-Methyl-1-vinylpyrimidine-2,4-diones (10a) and (10b): To a solution of 1-(2-bromoethyl)-pyrimidine-2,4-dione **9a** (1 mmol, 219 mg) or **9b** (1 mmol, 233 mg) in DMSO (8.8 mL) were added excesses of CH_3I (1.4 mL, 21 equiv.) and KOH (1.08 g, 19 equiv.) and the reaction mixture was stirred for 30 min. at 95 °C. After removal of all volatiles in vacuo, water (30 mL) was added and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo, and the crude product was purified by chromatography on silica gel to provide yellow crystals of **10a** and **10b**.

3-Methyl-1-vinyl-1*H*-pyrimidine-2,4-dione (10a): Yield: 128 mg (84%); m.p. 82–84 °C. – IR: ṽ = 3020, 1711, 1672, 1214, 746 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.32 (s, 3 H), 4.95 (dd, *J* = 9.0 and 2.1 Hz, 1 H), 5.06 (dd, *J* = 16.0 and 2.1 Hz, 1 H), 5.84 (dd, *J* = 8.1 Hz, 1 H), 7.21 (dd, *J* = 16.0 and 9.0 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 28.0, 101.5, 102.9, 130.7, 136.7, 149.8, 162.6. – $C_7H_8N_2O_2$ (152.15): calcd. C 55.26, H 5.30, N 18.41; found C 55.20, H 5.29, N 18.53.

3,5-Dimethyl-1-vinyl-1*H*-pyrimidine-2,4-dione (10b): Yield: 162 mg (97%); m.p. 87–89 °C. – IR: ṽ = 3018, 1674, 1642, 1215, 763 cm^{-1}.

– ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.97 (d, *J* = 1.2 Hz, 3 H), 3.34 (s, 3 H), 4.87 (dd, *J* = 9.1 and 2.1 Hz, 1 H), 5.03 (dd, *J* = 16.0 and 2.1 Hz, 1 H), 7.24 (dd, *J* = 16.0 and 9.1 Hz, 1 H), 7.31 (s, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 13.2, 28.0, 100.2, 111.0, 130.4, 132.5, 150.0, 163.3. – $C_8H_{10}N_2O_2$ (166.18): calcd. C 57.82, H 6.07, N 16.86; found C 57.75, H 6.10, N 16.89.

3-Benzoyl-5-methyl-1-vinyl-1*H*-pyrimidine-2,4-dione (7): To a stirred solution of **6**[18] (0.333 g, 1.45 mmol) in vinyl acetate (3.4 mL) under argon was added Na_2PdCl_4 (3.3 mg) and the mixture was heated under reflux for 8 h. After addition of activated charcoal (15 mg), the solution was shaken for 10 min., the solids were removed by filtration, and the filtrate was concentrated by distillation under high vacuum. The crude product was extracted with diethyl ether and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Recrystallization of the residue from $CHCl_3$ afforded **7** in the form of white crystals. Yield: 275 mg (74%); m.p. 147–149 °C. – IR: ṽ = 3021, 1750, 1709, 1663, 788, 756 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.02 (s, 3 H), 4.93 (dd, *J* = 9.1, 2.3 Hz, 1 H), 5.13 (dd, *J* = 16.2, 2.3 Hz, 1 H), 7.14 (dd, *J* = 16.0, 9.1 Hz, 1 H), 7.43 (s, 1 H), 7.47 (m, 2 H), 7.63 (m, 1 H), 7.92 (m, 2 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 12.6, 101.4, 112.1, 129.2, 129.5, 130.5, 131.5, 134.6, 135.2, 148.4, 162.6, 168.5. – $C_{14}H_{12}N_2O_3$ (256.26): calcd. C 65.62, H 4.72, N 10.93; found C 65.58, H 4.80, N 11.03.

Typical Procedure for Intramolecular Carbocyclization: Tributyltin hydride (4.5 mmol, 1.12 equiv.) was added to a degassed solution of the appropriate β-bromo alkynyl ether **17–22** (4 mmol) in dry benzene (10 mL) containing AIBN (30 mg). The mixture was refluxed for 2 h under argon atmosphere and then concentrated to dryness in vacuo. The residual oil was purified by chromatography on silica gel.

1-(4-Methylenetetrahydrofuran-2-yl)pyrrolidin-2-one (3a): Yield: 602 mg (90%). – IR: ṽ = 2956, 1690, 1682, 1045, 911 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.00 (m, 2 H), 2.36 (dd, *J* = 9.0 Hz and 8.5 Hz, 2 H), 2.49 (br. dd, *J* = 16.0 Hz and 6.9 Hz, 1 H), 2.77 (br. dd, *J* = 16.0 and 5.0 Hz, 1 H), 3.31 (ddd, *J* = 15.0 Hz, 10.4 Hz and 6.1 Hz, 1 H), 3.43 (ddd, *J* = 15.0 Hz, 9.5 Hz and 7.1 Hz, 1 H), 4.30 (dq, *J* = 13.3 Hz and 2.0 Hz, 1 H), 4.45 (dq, *J* = 13.3 Hz and 2.0 Hz, 1 H), 4.97 (quint., *J* = 2.2 Hz, 1 H), 5.04 (quint., *J* = 2.2 Hz, 1 H), 5.94 (dd, *J* = 6.9 and 5.0 Hz, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 17.9, 31.4, 35.3, 42.2, 70.8, 81.7, 105.7, 145.3, 175.7. – $C_9H_{13}NO_2$ (167.20): calcd. C 64.65, H 7.84, N 8.38; found C 64.53, H 7.90, N 8.43.

1-(4-Methylenetetrahydrofuran-2-yl)phthalimide (3b): Yield: 779 mg (85%). – IR: ṽ = 2980, 1685, 1660, 1085 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.97 (dd, *J* = 16.5 and 8.1 Hz, 1 H), 3.21 (dd, *J* = 16.5 and 4.6 Hz, 1 H), 4.38 (d, *J* = 12.5 Hz, 1 H), 4.60 (d, *J* = 12.5 Hz, 1 H), 5.01 (m, 1 H), 5.03 (m, 1 H), 6.10 (dd, *J* = 8.1 and 4.6 Hz, 1 H), 7.70 (m, 2 H), 7.77 (m, 2 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 35.4, 72.4, 80.7, 104.4, 123.4, 131.8, 134.2, 146.0, 167.7. – $C_{13}H_{11}NO_3$ (229.23): calcd. C 68.11, H 4.84, N 6.11; found C 68.15, H 4.92, N 6.05.

3-Methyl-1-(4-methylenetetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (23a): Yield: 375 mg (45%). – IR: ṽ = 3088, 2958, 1702, 1649, 1109 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 2.65 (m, 1 H), 3.12 (m, 1 H), 3.29 (s, 3 H), 4.53 (m, 2 H), 5.08–5.12 (m, 2 H), 5.73 (d, *J* = 8.1 Hz, 1 H), 6.14 (dd, *J* = 6.8 and 3.1 Hz, 1 H), 7.25 (d, *J* = 8.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 27.6, 38.8, 72.2, 87.1, 101.5, 107.9, 137.0, 142.5, 151.1, 163.0. – $C_{10}H_{12}N_2O_3$ (208.22): calcd. C 58.91, H 7.19, N 12.49; found C 58.73, H 7.26, N 12.34.

3,5-Dimethyl-1-(4-methylenetetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (23b): Yield: 444 mg (50%). – IR: ṽ = 2960, 1700, 1668, 1645, 1072 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.95 (s, 3 H), 2.63 (m, 1 H), 3.11 (m, 1 H), 3.31 (s, 3 H), 4.47 (m, *J* = 13 Hz, 1 H), 4.54 (m, *J* = 13 Hz, 1 H), 5.09–5.12 (m, 2 H), 6.19 (dd, *J* = 6.8 and 3.6 Hz, 1 H), 7.08 (s, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 13.6, 27.9, 38.7, 72.1, 86.8, 107.8, 110.0, 133.0, 143.2, 150.1, 160.6. – $C_{11}H_{14}N_2O_3$ (222.24): calcd. C 60.49, H 7.61, N 11.76; found C 60.36, H 7.72, N 11.66.

3,5-Dimethyl-1-(5-methyl-4-methylenetetrahydrofuran-2-yl)-(1*H*,3*H*)-pyrimidine-2,4-dione (24): Yield: 869 mg (92%). – IR: ṽ = 2956, 1703, 1695, 1644, 1079 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$) (mixture of diastereomers): δ = 1.39 and 1.42 (s, 3 H), 1.90 and 1.91 (s, 3 H), 2.54–2.69 (m, 1 H), 3.19 (m, 1 H), 3.29 and 3.33 (s, 3 H), 4.53–4.57 (m, 1 H), 4.97–5.05 (m, 2 H), 6.18 (m, 1 H), 7.12 and 7.13 (s, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 13.5 and 13.6, 19.6 and 21.4, 27.8 and 27.9, 38.5 and 38.7, 77.5 and 78.7, 83.6 and 85.8, 106.9 and 107.2, 109.6 and 110.1, 132.8 and 133.0, 147.9 and 148.1, 151.2 (2 C), 163.7 and 163.8. – $C_{12}H_{16}N_2O_3$ (236.27): calcd. C 61.00, H 6.83, N 11.86; found C 59.02, H 6.92, N 11.77.

3,5-Dimethyl-1-(5-prop-2-enyl-4-methylenetetrahydrofuran-2-yl)-(1*H*,3*H*)-pyrimidine-2,4-dione (25): Yield: 294 mg (28%). – IR: ṽ = 2926, 1692, 1664, 1639, 1091 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$) (mixture of diastereomers): δ = 1.80–1.72 (m, 3 H), 1.91 and 1.92 (d, *J* = 1.1 Hz, 3 H), 2.62 (dm, *J* = 16.8 Hz, 1 H), 3.21 (dm, *J* = 16.8 Hz, 1 H), 3.30 (s, 6 H), 4.83 (m, 1 H), 5.00–5.12 (m, 1 H), 5.45 (m, 1 H), 5.84 (m, 1 H), 6.19 (m, 1 H), 7.13 and 7.15 (d, *J* = 1.1 Hz, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 13.5 and 13.7, 17.7 and 17.9, 27.9 and 28.2, 38.6 and 38.7, 83.1 and 83.8, 84.0 and 86.1, 108.6 and 108.8, 109.7 and 110.1, 128.3 and 130.2, 129.2 and 132.7, 133.0 and 133.1, 146.2 (2 C), 151.2 (2 C), 163.7 and 164.1. – $C_{14}H_{18}N_2O_3$ (262.30): calcd. C 64.11, H 6.92, N 10.68; found C 64.18, H 7.03, N 10.59.

3,5-Dimethyl-1-(5,5-dimethyl-4-methylenetetrahydrofuran-2-yl)-(1*H*,3*H*)-pyrimidine-2,4-dione (26): Yield: 901 mg (90%). – IR: ṽ = 3014, 2959, 1699, 1667, 1638, 910 cm^{-1}. – ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.33 (s, 3 H), 1.45 (s, 3 H), 1.91 (d, *J* = 1.2 Hz, 3 H), 2.61 (ddt, *J* = 16.9, 5.2 and 2.2 Hz, 1 H), 3.23 (ddt, *J* = 16.9, 6.8 and 2.2 Hz, 1 H), 3.31 (s, 3 H), 4.94 (t, *J* = 2.2 Hz, 1 H), 4.99 (t, *J* = 2.2 Hz, 1 H), 6.19 (dd, *J* = 6.8 and 5.2 Hz, 1 H), 7.17 (q, *J* = 1.2 Hz, 1 H). – ^{13}C NMR (50.3 MHz, CDCl$_3$): δ = 13.5, 28.2, 27.9, 29.2, 38.6, 82.9, 83.9, 106.1, 110.2, 132.9, 150.1, 151.7, 163.7. – $C_{13}H_{18}N_2O_3$ (250.29): calcd. C 62.38, H 7.25, N 11.19; found C 62.24, H 7.33, N 10.92.

Intramolecular Carbocyclization of 22a: The cyclization was carried out according to the general procedure, starting from **22a** (150 mg); yield: 67 mg (55%) as an inseparable mixture of **27a/28a/29a** in the ratio 0.55:0.05:0.4.

***anti*-1-(5′Benzyloxymethyl-4-methylenetetrahydrofuran-2-yl)-3-methyl-(1*H*,3*H*)-pyrimidine-2,4-dione (27a):** ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.67 (m, 1 H, 2′β-H), 3.18 (m, 1 H, 2′α-H), 3.30 (s, 3 H, NCH$_3$), 3.54 (dd, *J* = 10.4 and 5.5 Hz, 1 H, 6′a-H), 3.60 (dd, *J* = 10.4 and 3.5 Hz, 1 H, 6′b-H), 4.58 (s, 2 H, 7′-H), 4.83 (m, 1 H, 4′-H), 5.09 (q, *J* = 2.0 Hz, 1 H, 5′a-H), 5.17 (q, *J* = 2.0 Hz, 1 H, 5′b-H), 5.73 (d, *J* = 8.1 Hz, 1 H, 5-H), 6.25 (dd, *J* = 7.0 and 2.7 Hz, 1 H, 1′-H), 7.27 (d, *J* = 8.1 Hz, 1 H, 6-H), 7.33 (m, 5 H, 9′-, 10′- and 11′-H).

***syn*-1-(5′-Benzyloxymethyl-4-methylenetetrahydrofuran-2-yl)-3-methyl-(1*H*,3*H*)-pyrimidine-2,4-dione (28a):** ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 2.60 (m, 1 H, 2′β-H), 3.21 (m, 1 H, 2′α-H), 3.30 (s, 3 H, NCH_3), 3.63 (dd, *J* = 10.4 and 3.5 Hz, 1 H, 6′α-H), 3.85 (dd, *J* = 10.4 and 2.8 Hz, 1 H, 6′β-H), 4.54 (s, 2 H, 7′-H), 4.62 (m, 1 H, 4′-H), 5.03 (q, *J* = 2.0 Hz, 1 H, 5′a-H), 5.16 (q, *J* = 2.0 Hz, 1 H, 5′b-H), 5.49 (d, *J* = 8.1 Hz, 1 H, 5-H), 6.25 (t, *J* = 6.5 Hz, 1 H, 1′-H), 7.31 (m, 5 H, 9′-, 10′- and 11′-H), 7.72 (d, *J* = 8.1 Hz, 1 H, 6-H).

Bicyclonucleoside (29a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, 13′-H), 1.56 (dd, *J* = 13.4 and 5.5 Hz, 1 H, 2′β-H), 1.67 (dd, *J* = 13.4 and 8.4 Hz, 1 H, 2′α-H), 3.25 (s, 3 H, NCH_3), 3.79 (dd, *J* = 11.0 and 4.2 Hz, 1 H, 5′β-H), 4.20 (d, *J* = 11.0 Hz, 1 H, 5′α-H), 4.33 (d, *J* = 4.2 Hz, 1 H, 4′-H), 4.44 (s, 1 H, 6′-H), 5.84 (d, *J* = 8.1 Hz, 1 H, 5-H), 6.12 (dd, *J* = 8.4 and 5.5 Hz, 1 H, 1′-H), 7.31 (m, 5 H, 8′-, 9′- and 10′-H), 7.50 (d, *J* = 8.1 Hz, 1 H, 6-H).

Intramolecular Carbocyclization of 22b: The cyclization was carried out according to the general procedure starting from **22b** (145 mg); yield: 73 mg (62%) as an inseparable mixture of **27b**/**28b**/**29b** in the ratio 0.55:0.05:0.4.

***anti*-1-(5′-Benzyloxymethyl-4-methylenetetrahydrofuran-2-yl)-3,5-dimethyl-(1*H*,3*H*)-pyrimidine-2,4-dione (27b):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (d, *J* = 1.2 Hz, 3 H, 7-H), 2.65 (m, 1 H, 2′β-H), 3.18 (m, 1 H, 2′α-H), 3.31 (s, 3 H, NCH_3), 3.54 (dd, *J* = 10.8 and 5.6 Hz, 1 H, 6′a-H), 3.59 (dd, *J* = 10.8 and 3.6 Hz, 1 H, 6′b-H), 4.58 (s, 2 H, 7′-H), 4.85 (m, 1 H, 4′-H), 5.09 (q, *J* = 2.0 Hz, 1 H, 5′a-H), 5.17 (q, *J* = 2.0 Hz, 1 H, 5′b-H), 6.24 (dd, *J* = 7.0 and 3.1 Hz, 1 H, 1′-H), 7.10 (q, *J* = 1.2 Hz, 1 H, 6-H), 7.33 (m, 5 H, 9′-, 10′- and 11′-H). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.5 (C-7), 27.8 (NCH_3), 39.1 (C-2′), 73.1 (C-6′), 73.7 (C-7′), 82.1 (C-4′), 86.6 (C-1′), 108.6 (C-5′), 109.8 (C-5), 127.7 (C-9′), 127.8 (C-11′), 128.6 (C-10′), 133.1 (C-6), 137.9 (C-8′), 144.2 (C-3′), 151.1 (C-2), 163.7 (C-4).

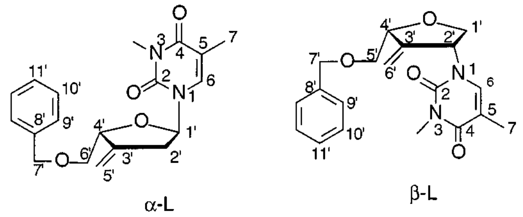
***syn*-1-(5′-Benzyloxymethyl-4-methylenetetrahydrofuran-2-yl)-3,5-dimethyl-(1*H*,3*H*)-pyrimidine-2,4-dione-(28b):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (d, *J* = 1.2 Hz, 3 H, 7-H), 2.68 (m, 1 H, 2′β-H), 3.22 (m, 1 H, 2′α-H), 3.30 (s, 3 H, NCH_3), 3.62 (dd, *J* = 11.2 and 4.0 Hz, 1 H, 6α-H), 3.86 (dd, *J* = 11.2 and 2.8 Hz, 1 H, 6′b-H), 4.58 (s, 2 H, 7′-H), 4.61 (m, 1 H, 4′-H), 4.99 (q, *J* = 2.0 Hz, 1 H, 5′a-H), 5.03 (q, *J* = 2.0 Hz, 1 H, 5′b-H), 6.25 (t, *J* = 6.7 Hz, 1 H, 1′-H), 7.31 (m, 5 H, 9′-, 10′- and 11′-H), 7.35 (q, *J* = 1.2 Hz, 1 H, 6-H). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.7 (C-7), 28.3 (NCH_3), 39.0 (C-2′), 72.5 (C-6′), 73.6 (C-7′), 80.8 (C-4′), 84.4 (C-1′), 107.9 (C-5′), 110.1 (C-5), 127.6 (C-9′), 127.8 (C-11′), 128.6 (C-10′), 133.7 (C-6), 137.7 (C-8′), 144.4 (C-3′), 151.3 (C-2), 163.7 (C-4).

Bicyclonucleoside (29b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, 13′-H), 1.56 (dd, *J* = 13.3 and 5.4 Hz, 1 H, 2′β-H), 1.68 (dd, *J* = 13.3 and 9.0 Hz, 1 H, 2′α-H), 1.98 (d, *J* = 1.2 Hz, 3 H, 7-H), 3.26 (s, 3 H, NCH_3), 3.79 (dd, *J* = 11.0 and 4.2 Hz, 1 H, 5′β-H), 4.22 (d, *J* = 11.0 Hz, 1 H, 5′α-H), 4.31 (d, *J* = 4.2 Hz, 1 H, 4′-H), 4.44 (s, 1 H, 6′-H), 6.12 (dd, *J* = 9.0 and 5.4 Hz, 1 H, 1′-H), 7.29 (q, *J* = 1.2 Hz, 1 H, 6-H), 7.32 (m, 5 H, 8′-, 9′- and 10′-H). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.5 (C-7), 23.3 (C-13′), 27.9 (NCH_3), 40.5 (C-2′), 54.1 (C-3′), 72.4 (C-5′), 85.8 (C-1′), 88.3 (C-6′), 90.2 (C-4′), 110.5 (C-5), 125.5 (C-8′), 127.9 (C-10′) 128.5 (C-9′), 132.7 (C-6), 137.5 (C-7′), 151.0 (C-2), 163.6 (C-4).

***anti*- and *syn*-1-(5′-Benzyloxymethyl-4-deuteriomethylenetetrahydrofuran-2-yl)-3,5-dimethyl-(1*H*,3*H*)-pyrimidine-2,4-dione (30 and 31):** Prepared from 60 mg (0.142 mmol) of **22b**; yield: 32 mg (65%) as an inseparable mixture of **30** and **31** in a ratio of 0.55:0.45.

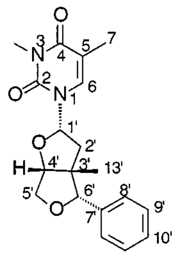
***anti* (30):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (d, *J* = 1.2 Hz, 3 H, 7-H), 2.65 (m, 1 H, 2′β-H), 3.18 (m, 1 H, 2′α-H), 3.31 (s, 3 H, NCH_3), 3.54 (dd, *J* = 10.8 and 5.6 Hz, 1 H, 6′a-H), 3.59 (dd, *J* = 10.8 and 3.6 Hz, 1 H, 6′b-H), 4.58 (s, 2 H, 7′-H), 4.85 (m, 1 H, 4′-H), 5.15 and 5.08 (m, 1 H, 5′-H), 6.24 (dd, *J* = 7.0 and 3.1 Hz, 1 H, 1′-H), 7.10 (q, *J* = 1.2 Hz, 1 H, 6-H), 7.33 (m, 5 H, 9′-, 10′- and 11′-H). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.5 (C-7), 27.8 (NCH_3), 39.1 (C-2′), 73.1 (C-6′), 73.7 (C-7′), 82.1 (C-4′), 86.6 (C-1′), 108.3 (t, *J* = 25 Hz, C-5′), 109.8 (C-5), 127.7 (C-9′), 127.8 (C-11′), 128.6 (C-10′), 133.1 (C-6), 137.8 (C-8′), 144.3 (C-3′), 151.1 (C-2), 163.7 (C-4).

***syn* (31):** 45% yield. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (d, *J* = 1.2 Hz, 3 H, 7-H), 2.68 (m, 1 H, 2′β-H), 3.22 (m, 1 H, 2′α-H), 3.30 (s, 3 H, NCH_3), 3.62 (dd, *J* = 11.2 and 4.0 Hz, 1 H, 6′a-H), 3.86 (dd, *J* = 11.2 and 2.8 Hz, 1 H, 6′b-H), 4.58 (s, 2 H, 7′-H), 4.61 (m, 1 H, 4′-H), 5.15 and 5.02 (m, 1 H, 5′-H), 6.25 (t, *J* = 6.7 Hz, 1 H, 1′-H), 7.31 (m, 5 H, 9′-, 10′- and 11′-H), 7.35 (q, *J* = 1.2 Hz, 1 H, 6-H). – ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 13.7 (C-7), 28.3 (NCH_3), 38.9 (C-2′), 72.5 (C-6′), 73.6 (C-7′), 80.8 (C-4′), 84.4 (C-1′), 107.6 (t, *J* = 25 Hz, C-5′), 110.1 (C-5), 127.6 (C-9′), 127.8 (C-11′), 128.6 (C-10′), 133.7 (C-6), 133.7 (C-8′), 144.4 (C-3′), 151.3 (C-2), 163.7 (C-4).



27a, $R^1 = R^2 = H$
27b, $R^1 = CH_3$, $R^2 = H$
30, $R^1 = CH_3$, $R^2 = D$

28a, $R^1 = R^2 = H$
28b, $R^1 = CH_3$, $R_2 = H$
31, $R^1 = CH_3$, $R^2 = D$



29a, R = H
29b, R = CH_3

Figure 2. NMR assignments

SmI_2-Promoted Carbocyclization of 22b to Methylenetetrahydrofurans (28b) and (29b): Diiodomethane (0.333 g, 1.24 mmol) was added dropwise to a suspension of samarium metal (0.230 g, 1.53 mmol) in dry THF (12 mL) under argon. A deep-blue color rapidly developed and the resulting solution was stirred at ambient temperature for 1 h. DMPU (0.6 mL) was then added, which resulted in a change of color to deep purple. Thereafter, a solution of **22b** (105 mg, 0.25 mmol) in THF (3 mL) containing *t*BuOH (0.06 mL) was slowly added and the resulting mixture was stirred at room temperature for 30 min. After filtration through silica gel and washing the collected solids with diethyl ether, the combined filtrate and washings were washed with brine and dried over $MgSO_4$. The crude product (71 mg, 83%) was found to consist of an inseparable mixture of methylenetetrahydrofurans *anti* **27b** and *syn* **28b** in a 1.2:1 ratio.

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