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# Photochemical Ring Expansion of 4-Azidouracil: a Route to 5*H*-1,3,5-Triazepin-2,4-dione in the Nucleoside Series

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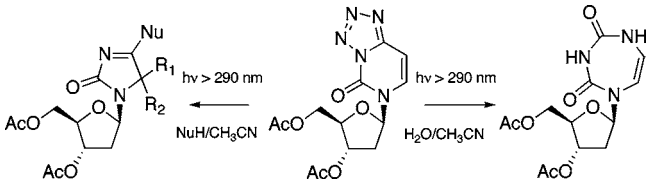
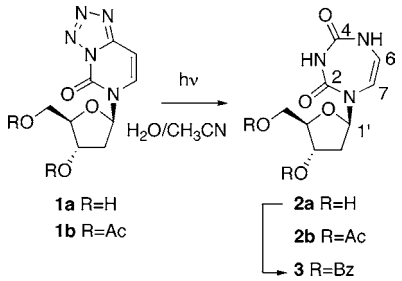



Under aqueous conditions, 4-azidouracil/tetrazolo[1,5-*c*]-pyrimidin-5(6*H*)-one nucleosides undergo a very efficient photochemical nitrogen elimination and ring expansion to 1,3,5-triazepin-2,4-dione nucleosides whose structure has been confirmed by X-ray crystallography. In contrast, when the photolysis was attempted under anhydrous conditions in the presence of a nucleophile, a ring contraction reaction occurred, affording 2-oxoimidazolone nucleosides. A mechanism to account for the formation of ring expansion and contraction reactions and involving a carbodiimide intermediate is proposed which is reminiscent of the known photochemical behavior of 2-azidopyridines/tetrazolo[1,5-*a*]-pyridines.

Base-modified nucleosides are powerful anticancer and antibiotic drugs. Among those, "base expanded nucleosides" look particularly promising.[1,2] However, in the pyrimidine analogue series, base expansion is currently limited to 1,3-diazepin-2-ones.[2] To increase the structural diversity of base-expanded nucleosides, we were interested in the direct enlargement of nucleobases within nucleosides. That would also present the advantage over the standard approach, to avoid the de novo synthesis of the aglycon moiety and then the glycosylation step.[2] While the photochemical synthesis of 1,3-diazepines from 2-azidopyridines/tetrazolo[1,5-*a*]pyridines is largely documented,[3] the synthesis of 1,3,5-triazepines from 4-azidopyrimidines/tetrazolo[1,5-*c*]pyrimidines has only been scarcely examined,[3a] although some known pyrimidine nucleoside analogues possess a 4-azidouracil/tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one aglycon moiety[4] closely related to 4-azidopyrimidines/tetrazolo[1,5-*c*]pyrimidines. Consequently, this prompted us to study the possible ring expansion of such pyrimidine nucleosides.

**SCHEME 1**




We report herein the highly efficient synthesis of the novel triazepine nucleosides (**2**) by photolysis of **1**.[4b] The X-ray crystal structure of **3**, the dibenzoyl analogue of **2**, and experiments aimed at exploring the photochemical reaction mechanism are also reported.

Photolysis[5] of the di-*O*-acetyl derivative of 6-(2-deoxy-$\beta$-D-ribosyl)tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one (**1b**, 4.5 mM) in water−acetonitrile (7:3) afforded **2b** ($UV_{MeOH}$: $\lambda_{max}$ 249 nm, $\epsilon_{249}$ 1936 $cm^{-1}\cdot mol^{-1}\cdot L$) in 80% yield after silica gel chromatography (Scheme 1).[6] The structure of **2b** was supported by spectroscopic data. Lack of modification on the sugar portion was inferred from its $^{13}C$ NMR spectrum, which displayed deoxyribose carbon signals similar to those of **1b**.

The HR mass data of **2b** (*m*/*z* 350.0944 $(M + Na)^+$) revealed the molecular formula $C_{13}H_{17}N_3O_7Na$ (calcd 350.0964) and sustained the $C_4H_4N_3O_2$ composition of the modified base moiety. NMR signals of the triazepine, attributed by 2D experiments, consisted of two exchangeable protons at $\delta$ 7.13 and 7.25, two olefinic protons at $\delta$ 5.77 and 5.73 whose attached carbon resonated at $\delta$ 115.0 and 111.3, respectively, and two quaternary carbons at $\delta$ 154.5 and 155.0. Carbon C2 ($\delta$ 154.5)

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(5) Pyrex-filtered light emitted by a 150 W high-pressure Hg lamp.

(6) Based on recovered starting material.

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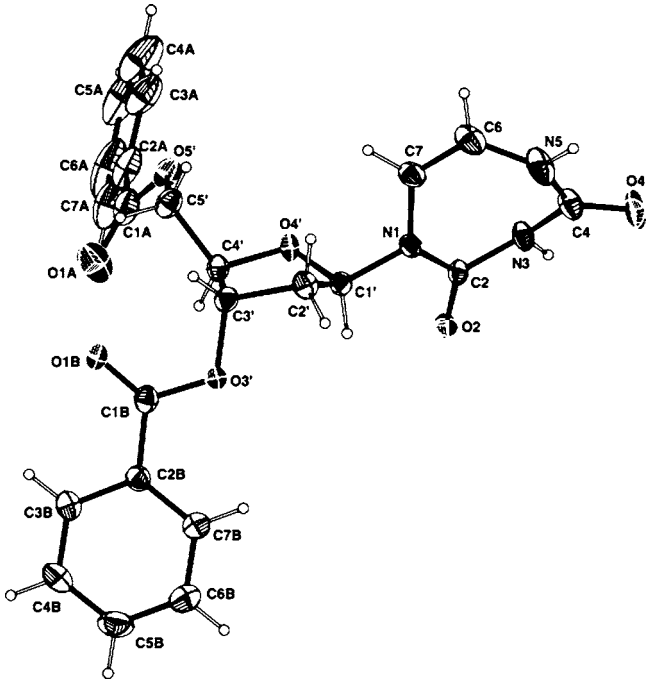


**FIGURE 1.** ORTEP drawing of X-ray structure of **3**. Ellipsoids are at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii.

and C7 ($\delta$ 111.3) were attributed from their $^3J$ coupling with proton H1′. Consequently, the resonance at $\delta$ 115.0 was attributed to C6. Surrounding of C2 and C4 ($\delta$ 155.0) by nitrogen atoms ($N^1$, $N^3$ and $N^3$, $N$,[5] respectively) was entirely consistent with their urea-type carbon chemical shift value. $N^3$H ($\delta$ 7.13) was identified from its $^3J$ correlation with C2 and C4, whereas $N^5$H ($\delta$ 7.25) was attributed from its coupling with H6.

To have an easy access to other diacylated analogues of **2** in view of X-ray crystallographic studies, the same photochemical reaction was reproduced in the deprotected series. Therefore, **1a**[4b] was photolyzed in water to afford **2a** (84% yield).[6] Dibenzoylation (PhCOCl, pyridine) of **2a** gave rise to **3** (77% yield), whose structure could be confirmed by X-ray crystallography (Figure 1). In this structure, the deoxyribose unit shows a rather unusual C1′-exo conformation ($P$ = 133.9°) and a maximum puckering amplitude, $\tau_m$ = 39.2°.[7] The modified base has a slightly twisted boat structure and adopts an anti glycosidic bond conformation ($\chi$ = −94.9°).

As in the 2-azidopyridine series in which a carbodiimide intermediate has been observed,[3d,8] the most probable mechanism accounting for the formation of **2b** involves carbodiimide **4** that is trapped with water to give **8** which spontaneously isomerizes (Scheme 2, Nu = OH). To further investigate the possible reaction of intermediate **4** with other nucleophiles such as alcohols or amines, we also photolyzed **1b** in the presence of diisopropylamine and methanol.

Photolysis of **1b** in diisopropylamine−acetonitrile (25:75) afforded 3′,5′-*O*-diacetyl-2′-deoxycytidine[9] and **5** in 49% and 21% yield, respectively.[6] The $^{13}$C NMR and HR MS data of **5** ($C_{18}H_{29}N_3O_6Na$; found 406.1946; calcd 406.1954) provided the base composition $C_9H_{14}N_3O$ which attested the loss of HCN, compared to **8** (Scheme 2, Nu = N($^i$Pr)$_2$). Recognition of $^1$H and $^{13}$C NMR signals corresponding to a N($^i$Pr)$_2$ group was straightforward ($^1$H: m, $\delta$ 3.87 and 3.69, 1H each and d, $\delta$ 1.66 and 1.38, 6H each; $^{13}$C: CH at $\delta$ 48.2 and 51.3, $CH_3$ at $\delta$ 20.5 and 19.7). The remaining carbon signals of the base-derived moiety of **5** appeared at $\delta$ 172.8 (quat C), 169.1 (quat C), and 46.1 ($CH_2$). Adjacency of the carbons at $\delta$ 169.1 and 46.1 to the $N^1$ atom was evidenced from their LR coupling with H1′ allowing their identification as C2 and C5, respectively. The remaining quaternary carbon ($\delta$ 172.8) was then attributed to C4 whose substitution with the N($^i$Pr)$_2$ group was confirmed by its $^3J$ correlation observed with each methine proton of the N($^i$Pr)$_2$ group. Taken altogether, these data supported the 2-imidazolone nature of the aglycone of **5**.

Photolysis of **1b**, carried out in methanol−dioxane (25:75) afforded two unseparable isomers **6a**,**b** (1/0.25 ratio, isolated yield 93%) whose $^1$H NMR spectra were highly similar.[6] The $^{13}$C NMR spectrum of **6a**,**b** suggested their belonging to the 2-imidazolone series (**6a**: $\delta$ C2 163.2 and $\delta$ C4 177.0), although HR MS ($C_{14}H_{19}N_3O_7Na$ (found 364.1127, calcd 364.1121) evidenced an isomery with **8** (Nu = $OCH_3$). The major differences between the NMR data of the modified base portion of **6** and **5** (considering the replacement of N($^i$Pr)$_2$ by a $CH_3O$ group) were (1) the lack of signals corresponding to a methylene group (C5 in **5**) and (2) the presence of a quaternary and an olefinic CH resonance ($\delta$ 105.8 and 125.8, respectively). The proton of this latter ($\delta$ 6.79) correlated with two exchangeable protons [$\delta$ 5.33 (d, $J$ = 10.9 Hz)]. This set of data supported the presence of an enamine group. As a consequence, the 1,4,5-trisubstituted-2-imidazolone structure was proposed for **6**. Observation of $^2J$ and $^3J$ correlations between H6 and C5 and C4, respectively, and of a $^3J$ correlation between H1′ and C2 and C5 ascertained the proposed structure.

In analogy with the mechanism proposed for the formation of **2b**, compounds **5** or **6** are likely to derive from triazepine **8** (Scheme 2). In anhydrous conditions, after UV-induced 4$\pi$ electrocyclization, this latter affords its transient bicyclic valence isomer **9** that subsequently undergoes a ring opening to give intermediate **10**. Evolution of **10** depends on the nucleophile. If Nu = $OCH_3$, imine **10** simply isomerizes to its more stable enamine form **6** whereas if Nu = N($^i$Pr)$_2$, HCN elimination leads to **5**.

Interestingly, a similar cascade of reactions leading to ring contraction has been very recently reported in the 2-azidopyridine series.[3d,e] Our results enlarge the scope of the intrinsic reactivity of 2-azidopyridines.

In summary, the photochemistry of 4-azidouracil nucleosides offers unprecedented opportunities for the synthesis of highly valuable 1,3,5-triazepin-2,4-dione nucleosides. These "fat pyrimidine" nucleosides, in addition to their potential as therapeutic agents, represent unique tools to subtlety probe the biophysical and biological properties of nucleic acids. Exploration of the possible extension of this photochemical reaction for other azido nucleosides is currently in progress in our Laboratory.

## Experimental Section

**1-(2-Deoxy-3,5-di-*O*,*O*′-acetyl-$\beta$-D-ribofuranosyl)-1,5-dihydro[1,3,5]triazepin-2,4-dione 2b.** Nucleoside **1b** (48 mg, 0.14 mmol) was dissolved in a water/acetonitrile solution (7/3; 31 mL)

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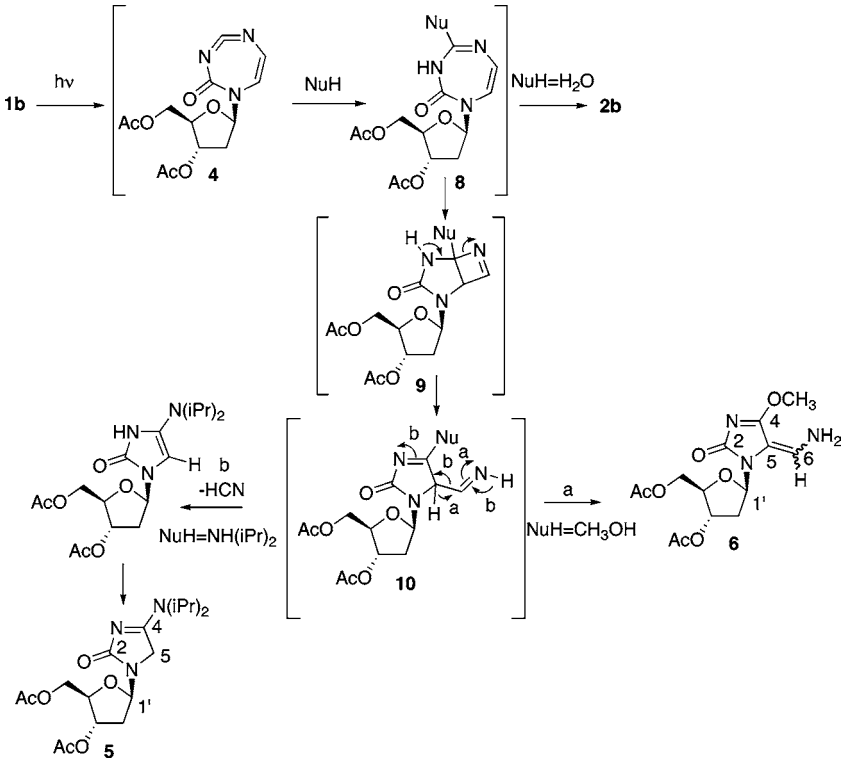
**SCHEME 2**




and degassed for 30 min under argon. Photolysis was carried out for 24 h. After evaporation of acetonitrile, the aqueous phase was saturated with NaCl and extracted with ethyl acetate (×3). The organic phases were combined, dried over $Na_2SO_4$, and concentrated to dryness. The crude product was purified by silica gel column chromatography using a gradient of methanol in dichloromethane (1% to 3%). Compound **2b** was obtained as a white solid (30 mg, 64%) together with recovered **1b** (9 mg, 19%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.25 (sl, 1H, *N*H5), 7.13 (s, 1H, *N*H3), 6.19 (dd, 1H, $J$ = 6.0; 8.7 Hz, H1′), 5.77 (m, 1H, H6), 5.73 (m, 1H, H7), 5.13 (td, 1H, $J$ = 2.5; 6.1 Hz, H3′), 4.25 (m, 2H, H5′H5″), 4.16 (m, 1H, H4′), 2.27−2.14 (m, 2H, H2′H2″), 2.09 (s, 6H, $CH_3$-Ac). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 170.5 (C═O-Ac × 2), 155.0 (C4), 154.5 (C2), 115.0 (C6), 111.3 (C7), 85.5 (C1′), 81.3 (C4′), 74.2 (C3′), 64.1 (C5′), 35.3 (C2′), 21.0/20.9 ($CH_3$-Ac × 2). HRMS (ESI, MeOH, (M + Na)$^+$): calcd for $C_{13}H_{17}N_3O_7Na$ 350.0964, found 350.0944.

**1-(2-Deoxy-β-D-ribofuranosyl)-1,5-dihydro[1,3,5]triazepin-2,4-dione 2a.** An aqueous solution (260 mL) of nucleoside **1a** (100 mg, 0.39 mmol) was degassed for 30 min under argon and photolyzed for 16 h. After concentration and lyophilization, the residue was purified by silica gel column chromatography using a gradient of methanol in dichloromethane (3% to 20%). Compound **2a** was obtained as a white solid (70 mg, 72%) together with recovered **1a** (14 mg, 14%). $^1$H NMR (300 MHz, $D_2O$): $\delta$ 6.08 (t, 1H, $J$ = 7.2 Hz, H1′), 5.89 (d, 1H, $J$ = 6.3 Hz, H6), 5.77 (d, 1H, $J$ = 6.3 Hz, H7), 4.34 (td, 1H, $J$ = 3.7; 7.0 Hz, H3′), 3.90 (m, 1H, H4′), 3.78−3.64 (m, 2H, H5′H5″), 2.29 (m, 1H, H2′$^a$), 2.13 (m, 1H, H2″$^a$). $^a$: interchangeable attributions. $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ 157.4/157.2 (C4,C2), 116.6 (C6), 112.4 (C7), 86.1/86.0 (C1′,C4′), 71.2 (C3′), 62.1 (C5′), 37.0 (C2′). HRMS (ESI, MeOH, (M + Na)$^+$): calcd for $C_9H_{13}N_3O_5Na$ 266.0753, found 266.0760.

**1-(2-Deoxy-3,5-di-*O*,*O*′-benzoyl-β-D-ribofuranosyl)-1,5-dihydro[1,3,5]triazepin-2,4-dione 3.** Compound **2a** (40 mg, 0.16 mmol) was coevaporated with anhydrous pyridine (×2) and then dissolved in pyridine (1.6 mL). Benzoyl chloride (57 μL, 0.49 mmol) was added and the reaction mixture stirred at room temperature for 3 h. After evaporation and coevaporation with toluene, the crude mixture was dissolved in dichloromethane and washed with water. The organic phases were combined and dried over $Na_2SO_4$ and concentrated to dryness. Purification was achieved by silica gel column chromatography using a gradient of methanol in dichloromethane (0−5%). Compound **3** was obtained as a white solid (57 mg, 77%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.06−8.02 (m, 4H, H-Bz), 7.62−7.43 (m, 6H, H-Bz), 7.35 (sl, 1H, *N*H5), 7.19 (s, 1H, *N*H3), 6.34 (m, 1H, H1′), 5.75 (d, 1H, $J$ = 6.2 Hz, H7), 5.55 (m, 2H, H6, H3′), 4.63 (m, 2H, H5′H5″), 4.46 (m, 1H, H4′), 2.40 (m, 2H, H2′H2″). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 166.2/166.1 (C═O-Bz × 2), 155.2 (C4), 154.6 (C2), 133.7−128.6 (C-Bz), 115.1 (C6), 111.4 (C7), 85.7 (C1′), 81.7 (C4′), 75.0 (C3′), 64.6 (C5′), 35.7 (C2′). HRMS (ESI, MeOH, (M + Na)$^+$): calcd for $C_{23}H_{21}N_3O_7Na$ 474.1277, found 474.1259.

**1-(2-Deoxy-3,5-di-*O*,*O*′-acetyl-β-D-ribofuranosyl)-4-*N*,*N*-diisopropylamino-1,5-dihydroimidazol-2-one 5.** Nucleoside **1b** (30 mg, 0.09 mmol) was dissolved in a mixture of acetonitrile and *N*,*N*-diisopropylamine (3/1, 60 mL). The solution was then degassed for 30 min under argon and photolyzed for 20 h. After evaporation, the crude product was purified by silica gel column chromatography using a gradient of methanol in dichloromethane (1−10%). Compound **5** was obtained as a slightly yellow film (5.1 mg, 15%) along with 3′,5′-*O*-diacetyl-2′-deoxycytidine (9.8 mg, 35%) and recovered **1b** (8.4 mg, 28%). $^1$H NMR (400 MHz, $CDCl_3$ + $C_6D_6$): $\delta$ 6.35 (dd, 1H, $J$ = 9.1; 5.7 Hz, H1′), 5.24 (m, 1H, H3′), 4.37 (m, 2H, H5′H5″), 4.32 (d, 1H, $J$ = 15.4 Hz, H5a), 4.25 (m, 1H, H4′), 4.03 (d, 1H, $J$ = 15.4 Hz, H5b), 3.87 (m, 1H, H-$^i$Pr), 3.69 (hp, 1H, $J$ = 6.7 Hz, H-$^i$Pr), 2.26 (m, 2H, H2′H2″), 2.21 (2s, 6H, $CH_3$-Ac × 2), 1.66 (d, 6H, $J$ = 6.7 Hz, $CH_3$-$^i$Pr × 2), 1.38 (d, 6H, $J$ = 6.3 Hz, $CH_3$-$^i$Pr × 2). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ 172.8 (C4), 170.7 (C═O-Ac × 2), 169.1 (C2), 82.4 (C1′), 80.0 (C4′), 74.4 (C3′), 64.4 (C5′), 51.3 (CH-$^i$Pr), 48.2 (CH-$^i$Pr), 46.1 (C5), 34.8 (C2′), 21.1/20.9 ($CH_3$-Ac × 2), 20.5/19.7 ($CH_3$-$^i$Pr × 2). HRMS (ESI, MeOH, (M + Na)$^+$): calcd for $C_{18}H_{29}N_3O_6Na$ 406.1954, found 406.1946.

**5-(1-Aminoethylidenyl)-1-(2-deoxy-3,5-di-*O*,*O*′-acetyl-β-D-ribofuranosyl)-1,5-dihydro-4-methoxyimidazol-2-one 6.** Nucleoside **1b** (60 mg, 0.18 mmol) was dissolved in a mixture of dioxane−methanol (75/25; 120 mL) and degassed for 30 min under argon.

The solution was photolyzed for 44 h. After evaporation of the solvents, the residue was purified by silica gel column chromatography using a gradient of methanol in dichloromethane (2−4%). Compound **6** was obtained as a slightly yellow solid (15 mg, 25%) as a mixture of two diastereomers (ratio 1:5) together with recovered **1b** (44 mg, 73%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.89 (t, 0.17H, $J$ = 10.9 Hz, H1″*), 6.79 (t, 0.83H, $J$ = 10.9 Hz, H1″), 6.16 (dd, 0.83H, $J$ = 10.0; 5.2 Hz, H1′), 6.07 (dd, 0.17H, $J$ = 9.3; 5.6 Hz, H1′*), 5.33 (dl, 1.66H, $NH_2$), 5.12 (m, 1H, H3′, H3′*), 4.98 (dl, 0.34H, $NH_2$*), 4.53 (dd, 0.83H, $J$ = 5.2; 12.3 Hz, H5′a), 4.38−4.26 (m, 1.17H, H5′b, H5′a*, H5′b*), 4.16 (s, 0.51H, $OCH_3$*), 4.09 (m, 1H, H4′, H4′*), 4.04 (s, 2.49H, $OCH_3$), 2.67 (ddd, 0.17H, $J$ = 7.4 Hz; 14.5; 9.3 Hz, H2′a*[a]), 2.31 (m, 0.83H, H2′a[a]), 2.20−2.12 (m, 1H, H2′b, H2′b*[a]), 2.10−2.09 (2s, 6H, $CH_3$-Ac × 2, $CH_3$-Ac* × 2). [a]: interchangeable attributions. *: minor diastereomer. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 177.0 (C4), 170.7/170.4 (C═O-Ac × 2), 163.3 (C2), 125.8 (C1″), 105.8 (C5), 82.7 (C1′), 80.3 (C4′), 72.5 (C3′), 63.0 (C5′), 56.9 ($OCH_3$), 36.4 (C2′), 21.0/20.9 ($CH_3$-Ac × 2). HRMS (ESI, MeOH, $(M + Na)^+$): calcd for $C_{14}H_{19}N_3O_7Na$ 364.1121, found 364.1127.

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**Supporting Information Available:** General information, NMR spectra of compounds **2**, **3**, **5**, and **6**; X-ray crystallographic data for **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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