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Synthesis of adenosine-based fluorosides containing a novel heterocyclic ring system

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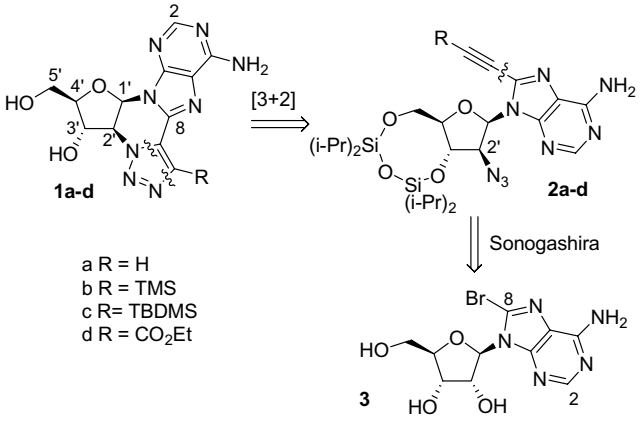
Abstract—A novel class of fluorescent adenosine derivatives (fluorosides) containing the previously unreported 8-(3*H*-[1,2,3]triazol-4-yl)-9*H*-purine heterocyclic ring system is reported, with Sonogashira cross-coupling and [3+2]-cycloaddition reactions being the key steps in the synthesis.

As an adjunct to a current project involving the identification of novel inhibitors of pathogenic organisms' tRNA synthetases, we have become interested in adenosine derivatives possessing an additional 'bridging' ring between the heterocyclic purine base and the 2′-position of the ribose sugar (nucleoside numbering). The current interest in so-called 'click chemistry' reactions,[1] especially the copper-catalysed [3+2]-cycloaddition of alkynes and azides,[2] led us to consider the use of the 1,2,3-triazole ring as a means of bridging the base and sugar moieties of adenosine (Scheme 1, **1a**–**d**).



Scheme 1. Retrosynthetic analysis and numbering scheme.

Our approach to the resultant pentacyclic nucleosides of general structure **1** is shown in Scheme 1. The 1,2,3-triazole ring was to be constructed using a Huisgen-type [3+2]-cycloaddition[3] of an alkyne and an azide. The requisite alkyne substituent may be installed in the 8-position (nucleoside numbering) of a suitably protected derivative of 8-bromoadenosine **3**[4] by a Sonogashira cross-coupling reaction.[5] This allows the 4-substituent of the 1,2,3-triazole ring to be easily varied, through the use of various terminal alkynes. This, in turn, enables the electronic and steric (and consequently optical) properties of the final compounds to be tuned if desired.

The synthesis of the parent fluoroside[6] **1a** (R = H) is shown in Scheme 2. Coupling of ethynyltrimethylsilane with aryl bromide **4**[7] using $Pd(PPh_3)_2Cl_2$ as palladium source proceeded smoothly to afford the desired product **5b** in 78% yield. Triflation of the 2′-hydroxyl group of **5b** was accomplished in 93% yield using trifluoromethanesulfonyl chloride and DMAP in dichloromethane at 0 °C. The crude triflate was used directly without purification. An initial attempt at S_N2 displacement of the 2′-triflate of **8b** by sodium azide did not afford the expected azide **2b**. Instead, after 3 h at room temperature, desilylated triflate **9** (the identity of which was confirmed by its direct synthesis from compound **5b** by desilylation and 2′-*O*-triflation, Scheme 2) and desilylated triazole **10** were isolated in 34% and 28% purified yields respectively, along with recovered starting material **8b**. 1,4-Disubstituted 1,2,3-triazole **10** was characterised by the appearance of a singlet at δ 8.47 ppm in the proton NMR spectrum as well as a brightly fluorescent spot on a TLC plate (when visualised with a 366 nm UV lamp).

Keywords: Cycloaddition; Palladium; Cross-coupling; Nucleosides.
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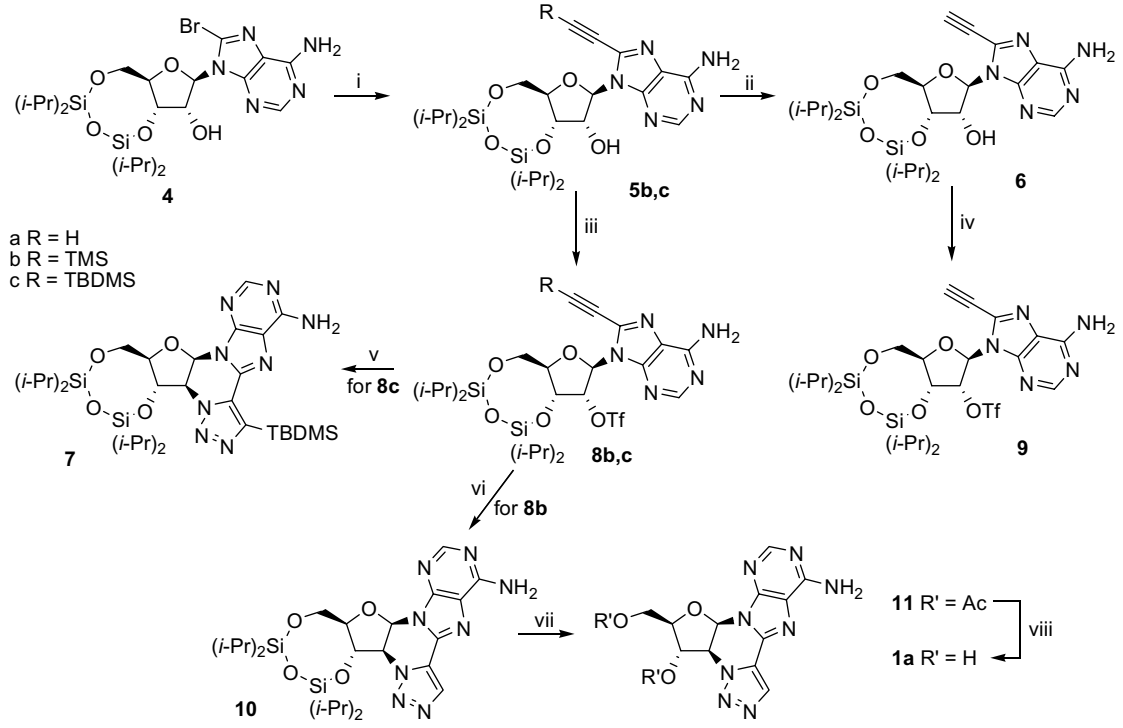


Scheme 2. Reagents and conditions: (i) TMS acetylene (4 equiv) or TBDMS acetylene (4 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (20 mol%), NEt_3 (4 equiv), THF, rt, 16 h, 78% (R = TMS), 79% (R = TBDMS); (ii) aq NH_3, MeOH, rt, 3 h, 49%; (iii) CF_3SO_2Cl, DMAP, CH_2Cl_2, 93% (R = TMS), 96% (R = TBDMS); (iv) CF_3SO_2Cl, DMAP, CH_2Cl_2, 81% crude; (v) NaN_3 (5 equiv), DMF, rt, 21 h, 30%; (vi) NaN_3 (5 equiv), DMF, rt, 75%; (vii) (a) NH_4F, MeOH, 60 °C, 4 h, (b) Ac_2O, pyridine, 16 h, rt, 82% for two steps; (viii) 7 N NH_3 in MeOH, rt, 19 h, quant.

Obviously, removal of the TMS group of alkynylsilane **8b** by sodium azide is faster than displacement of the 2′-triflate. In the *ribo*-configured **8b**, the azide anion must attack the 2′ carbon from the same face of the ribose ring as the purine base, which leads to significant reduction of the reaction rate. The corresponding displacement of an *arabino*-configured 2′-triflate by azide is complete in 2 h at room temperature.[8] Increasing the reaction time to 21 h led to the complete conversion (by silica gel TLC) of compound **8b** to triazole-containing fluoroside **10**, which was isolated in 75% yield after column chromatography.

The removal of the TMS group of **8b** by sodium azide, while serendipitous (in that it removes the need for a separate deprotection step) for the synthesis of compound **1a** is unfortunate in other respects. Electrophilic substitution of an arylsilane could, in theory, furnish an aryl iodide for use in further metal-catalysed cross-coupling reactions. The feasibility of such a 'late-stage scaffold' approach was briefly investigated. Sonogashira cross-coupling of bromide **4** with (*tert*-butyldimethylsilyl)acetylene afforded the TBDMS-protected alkyne **5c** in 79% yield. 2′-*O*-Triflation using trifluoromethanesulfonyl chloride and DMAP afforded 2′-*O*-triflate **8c** in 96% crude yield (after aqueous work-up), and this was employed in the next step without further purification. S_N2-type displacement of the triflate of **8c** with sodium azide at room temperature for 170 h afforded the desired arylsilane **7** in 30% yield after chromatographic purification, along with unreacted starting material (20% recovered), desilylated compound **10** and several unidentified by-products. Attempts to shorten the reaction time by the use of microwave heating led to exclusive formation of desilylated **10**. In addition, no electrophilic substitution of the arylsilane **7** was observed on prolonged reaction (1 week) with excess iodine monochloride.

The fluorescence of compound **10** was of interest and may be attributed to extended π-conjugation between the purine ring system and the newly formed triazole ring. A quantum yield of 0.68 was measured for compound **10** in methanol, using quinine sulfate[9] as the reference fluorophore. However, despite this rather efficient fluorescence, the majority of the emission is in the UV region (Fig. 1).

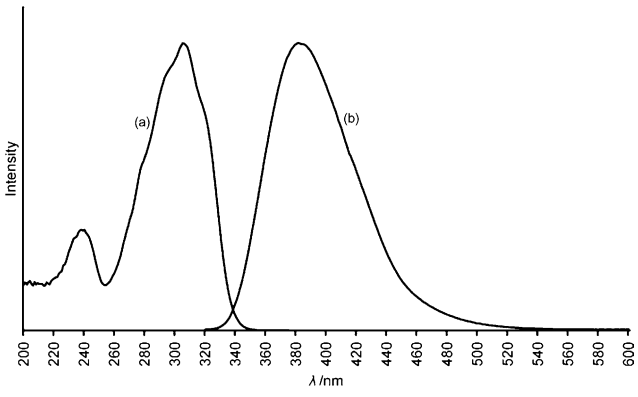


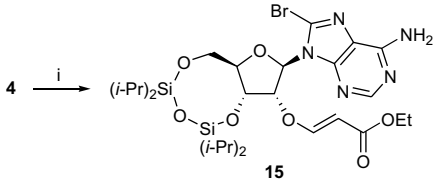
Figure 1. Normalised fluorescence excitation (a) and emission (b) spectra of fluoroside **1a** in methanol.

Removal of the 3′,5′-*O*-TIPDS protecting group of **10** was accomplished by treatment with ammonium fluoride in methanol[10] at 60 °C for 4 h. The resulting diol was too polar (and water soluble) to be isolated or purified directly using standard work-up and purification procedures. Diacetylation of the crude diol using acetic anhydride in pyridine afforded diacetate **11** in 82% yield from compound **10**. This could be purified by silica gel column chromatography. Subsequent deacetylation was accomplished using 7 N ammonia in methanol, affording pure diol **1a** in quantitative yield without the need for chromatographic purification.[11]

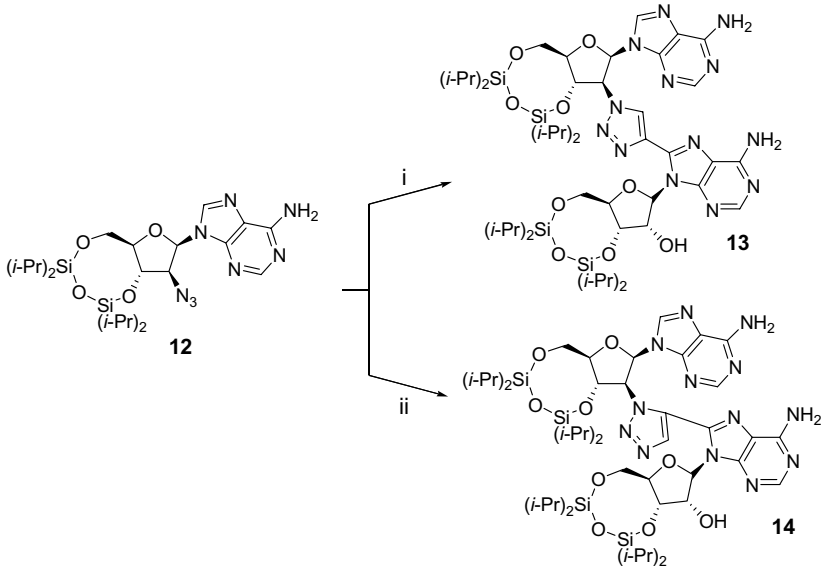
The unexpected room-temperature cycloaddition involving the unactivated alkyne of **8b** was attributed to intramolecularity. To confirm this, or indeed to investigate if the electron-deficient purine ring system provided sufficient activation of the alkyne, the intermolecular counterpart of this reaction was carried out (Scheme 3). A solution of azide **12**[8] and terminal alkyne **6** in chloroform was heated to reflux for 72 h, with TLC analysis showing that no reaction had occurred after this time. In refluxing toluene, a mixture of the two possible regioisomers (**13**, 18% and **14**, 31% purified yields[12]) was obtained after 140 h. Regiochemistry was initially assigned on the basis of the chemical shifts of the 1,2,3-triazole ring proton, with the proton of the 1,5-regioisomer **14** occurring upfield (δ 7.73 ppm) of the corresponding proton in 1,4-regioisomer **13** (δ 8.04 ppm).[2b,13] The Cu^{I}-catalysed [3+2]-cycloaddition reaction (which is known to give only the 1,4-regioisomer[2]) of azide **12**[8] and alkyne **6** afforded a single 1,2,3-triazole regioisomer in 73% purified yield (Scheme 3). The triazole produced by this copper-catalysed method exhibited a singlet at δ 8.04 ppm in the ^{1}H NMR spectrum, confirming the regiochemical assignment of the products from the thermal cycloaddition of azide **12** and alkyne **6**.

An electron-withdrawing substituent (e.g., carboethoxy) on the triazole ring (compound **1d**) should be expected to red-shift the UV absorption (and hence fluorescence emission), that is, closer to the visible range. Attempts to cross-couple aryl bromide **4** with ethyl propiolate failed, affording enol ether **15** as the sole product in 79% yield (Scheme 4).[14] The trans configuration of the double bond was assigned on the basis of the 12.3 Hz coupling constant between the olefinic protons. A similar failed outcome of an attempt to cross-couple ethyl propiolate with a nucleoside-derived aryl halide containing free-hydroxyl groups has been reported by Matsuda et al.[15]

In conclusion, we have developed a synthetic route to a new class of adenosine-based fluorosides possessing a previously unreported heterocyclic skeleton. A series of compounds of general structure **1** (including **1d**) is currently being synthesised, and in addition, an oligonucleotide containing fluoroside **1a** is currently being synthesised. The results of these investigations will be reported in due course.



Scheme 4. Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, ethyl propiolate, THF, rt, 16 h, 79%.



Scheme 3. Reagents and conditions: (i) 1 equiv **6**, $CuSO_4 \cdot 5H_2O$ (1 mol%), sodium ascorbate (10 mol%), 1:1 *t*-BuOH–H_2O, rt, 20.5 h, 73%; (ii) 1 equiv **6**, toluene, reflux, 140 h.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.115.

References and notes

1. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137.
2. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
3. Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613–628; Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494–2507; Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, 1984; Vol. 1, pp 559–651; Sha, C.-K.; Mohanakrishnan, A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley: New York, 2002, pp 623–679. For 1,3-dipolar cycloadditions employing azides in the preparation of carbohydrate derivatives: Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 771–797; Hotha, S.; Anegundi, R. I.; Natu, A. A. *Tetrahedron Lett.* **2005**, *46*, 4585–4588.
4. Ikehara, M.; Kaneko, M. *Tetrahedron* **1970**, *26*, 4251–4259.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 521; (b) For Sonogashira cross-coupling reactions involving nucleosides see Lambertucci, C.; Constanzi, S.; Vittori, S.; Volpini, R.; Cristalli, G. *Nucleosides Nucleotides* **2001**, *20*, 1153–1157; Flasche, W.; Cismas, C.; Herrmann, A.; Liebscher, J. *Synthesis* **2004**, 2335–2341.
6. Gao, J.; Strässler, C.; Tahmassebi, D.; Kool, E. T. *J. Am. Chem. Soc.* **2002**, *124*, 11590–11591.
7. Maruyama, T.; Kozai, S.; Manabe, T.; Yazima, Y.; Satoh, Y.; Takaku, H. *Nucleosides Nucleotides* **1999**, *18*, 2433–2442.
8. Robins, M. J.; Hawrelak, S. D.; Hernández, A. E.; Wnuk, S. W. *Nucleosides Nucleotides* **1992**, *11*, 821–834.
9. Melhuish, W. H. *J. Phys. Chem.* **1961**, *65*, 229–235.
10. Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177–1180.
11. Compound **1a**: $[\alpha]_D^{20}$ 11.5 (*c* 0.08, DMF); λ_{max} (MeOH)/nm 235 (ε/dm^3 mol^{-1} cm^{-1} 15 420), 307 (22 140); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 8.45 (s, 1H), 8.27 (s, 1H), 7.67 (br s, 2H, D_2O exchangeable), 6.61 (d, 1H, $J = 4.4$ Hz), 6.43 (d, 1H, $J = 5.2$ Hz, D_2O exchangeable), 5.29 (d, 1H, $J = 4.4$ Hz), 5.07 (dd, 1H, $J = 5.2$, 2.7 Hz), 4.77 (t, 1H, $J = 5.7$ Hz, D_2O exchangeable), 4.02 (td, 1H, $J = 5.2$, 2.7 Hz), 3.00–3.11 (2 × m, 2H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 156.1, 153.9, 149.3, 135.5, 130.1, 125.6, 119.2, 86.7, 79.7, 75.6, 64.9, 60.6; IR (cm^{-1}, KBr disk) 3343, 3215, 2916, 1648, 1597, 1576, 1495, 1298, 1095, 1036, 971, 923. Anal. Calcd for $C_{12}H_{12}N_8O_3$: C, 45.6; H, 3.8; N, 35.4. Found: C, 45.4; H, 3.9; N, 35.3.
12. Compound **13**: $[\alpha]_D^{20}$ −130.8 (*c* 0.09, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 8.20 (s, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 8.03 (s, 1H), 6.67 (d, 1H, $J = 5.8$ Hz), 6.18 (s, 1H), 5.64 (t, 1H, $J = 8.2$ Hz), 5.46–5.58 (m, 6H), 5.04 (d, 1H, $J = 5.5$ Hz), 4.41 (dd, 1H, $J = 12.8$, 2.9 Hz), 4.16–4.23 (m, 2H), 4.02–4.09 (m, 3H), 3.21 (br s, 1H), 0.97–1.21 (m, 53H), 0.51–0.53 (m, 3H); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 155.8, 153.4, 153.0, 150.4, 148.9, 142.0, 138.4, 138.0, 127.3, 119.9, 119.5, 90.1, 82.9, 82.4, 74.2, 72.1, 71.2, 68.5, 62.7, 60.7, 17.7, 17.6, 17.5, 17.4, 17.3, 17.23, 17.18, 16.9, 16.5, 13.8, 13.4, 13.3, 13.2, 13.0, 12.8, 12.4; IR (cm^{-1}, KBr disk) 3375, 2946, 2868, 1639, 1583, 1466, 1386, 1332, 1294, 1248, 1209, 1150, 1038, 885, 777, 701, 601, 456. Anal. Calcd for $C_{46}H_{77}N_{13}O_9Si_4$: C, 51.7; H, 7.3; N, 17.0. Found: C, 51.5; H, 7.4; N, 16.9. Compound **14**: $[\alpha]_D^{20}$ −228.9 (*c* 0.07, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 8.24 (s, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 7.73 (s, 1H), 7.22 (d, 1H, $J = 7.3$ Hz), 6.07 (t, 1H, $J = 8.6$ Hz), 5.73 (s, 1H), 5.66 (t, 1H, $J = 8.1$ Hz), 5.46–5.50 (m, 1H), 5.42 (br s, 2H), 5.26 (d, 1H, $J = 5.5$ Hz) 4.28 (dd, 1H, $J = 13.2$, 2.7 Hz), 4.19 (dd, 1H, $J = 13.0$, 2.8 Hz), 3.91–4.10 (m, 4H), 3.11 (br s, 1H), 0.96–1.30 (m, 53H), 0.64 (d, 3H, $J = 7.7$ Hz); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 156.6, 155.8, 153.9, 153.0, 150.0, 139.2, 138.5, 135.1, 128.4, 120.3, 118.9, 89.7, 52.4, 82.1, 81.4, 73.5, 72.5, 71.7, 68.3, 62.1, 60.6, 17.62, 17.57, 17.50, 17.47, 17.43, 17.40, 17.3, 17.21, 17.15, 17.09, 16.86, 16.88, 13.9, 13.3, 13.2, 12.9, 12.8, 12.7, 12.6; IR (cm^{-1}, KBr disk) 3386, 2945, 2868, 2365, 1640, 1583, 1466, 1420, 1367, 1332, 1293, 1249, 1213, 1146, 1037, 952, 885, 777, 700, 602, 453.
13. Alonso, G.; Garcia-López, M. T.; García-Munõz, G.; Madroñero, R.; Rico, R. *J. Heterocycl. Chem.* **1970**, *7*, 1272–1296.
14. Compound **15**: $[\alpha]_D^{20}$ −37.8 (*c* 0.75, $CHCl_3$); ^{1}H NMR [$CDCl_3$, 400 MHz]: δ 8.22 (br s, 1H), 7.58 (d, 1H, $J = 12.3$ Hz), 6.03 (s, 1H), 5.60 (br s, 2H), 5.48–5.53 (m, 2H), 5.45 (d, 1H, $J = 5.5$ Hz), 5.33 (d, 1H, $J = 12.3$ Hz), 4.15 (q, 2H, $J = 7.2$ Hz), 4.08 (dd, 1H, $J = 13.4$, 2.7 Hz), 3.95–4.04 (m, 1H), 1.25 (t, 3H, $J = 7.2$ Hz), 0.92–1.22 (28H, m); ^{13}C NMR [$CDCl_3$, 100 MHz]: δ 167.5, 162.2, 150.5, 129.9, 128.8, 128.7, 128.4, 128.2, 98.8, 88.6, 83.0, 81.4, 70.4, 60.3, 60.0, 17.6, 17.49, 17.46, 17.4, 17.06, 17.02, 14.5, 13.5, 13.1, 12.9, 12.8; IR (cm^{-1}, KBr disk) 3334, 3181, 1713, 1644, 1598, 1462, 1368, 1322, 1289, 1192, 1131, 1037, 885, 856, 777, 695; *m/z* (FAB) 686.211 (M^++1. $C_{27}H_{45}BrN_5O_7Si_2$ requires 686.204).
15. Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. *J. Med. Chem.* **1992**, *35*, 241–252.