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Hetero Diels−Alder Synthesis of 3-Hydroxypyridines: Access to the Nosiheptide Core

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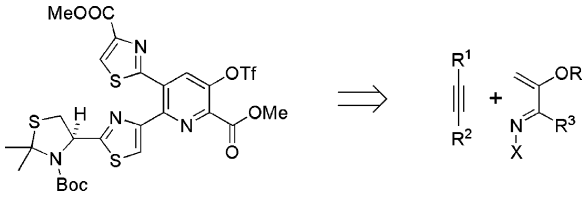
Received February 20, 2007



The 1-azadiene hetero Diels−Alder reaction of silylated enol oximes with alkynes was investigated and was optimized to furnish 2,5,6-trisubstituted 3-hydroxypyridines in high yields in one simple operation. Importantly, monosubstituted alkynyl ketones were found to lead to the formation of the 6-isomer with exceptional regioselectivity (>95:5). This methodology was applied to a scaleable synthesis of the core structure of the potent antibiotic nosiheptide. Protecting groups were optimized, which led to a racemization-free seven-step synthesis of the key building block.

Introduction

3-Hydroxypyridines[1] are important scaffolds in very diverse bioactive substances (Figure 1). Pyridoxin (**1**, vitamin B6) is a vital cofactor for the enzymes of amino acid metabolism.[2] Both the natural 3-hydroxypyridines, such as caerulomycin B[3] (**2**), as well the as non-natural congeners, such as persynthamide[4] (**3**), are endowed with distinctive modes of action. Remarkably, a 3-hydroxypyridine core is characteristic for the thiopeptide antibiotics nosiheptide[5] (**4**) and nocathiacin,[6] which are arguably the most potent within the thiopeptide antibiotic class.[7] In terms of their molecular properties, 3-hydroxypyridines cannot form an energetically favored keto tautomer, like the closely related 2- and 4-hydroxypyridines can, which leads to a much more phenolic character of the parent heterocycle. On the other hand,

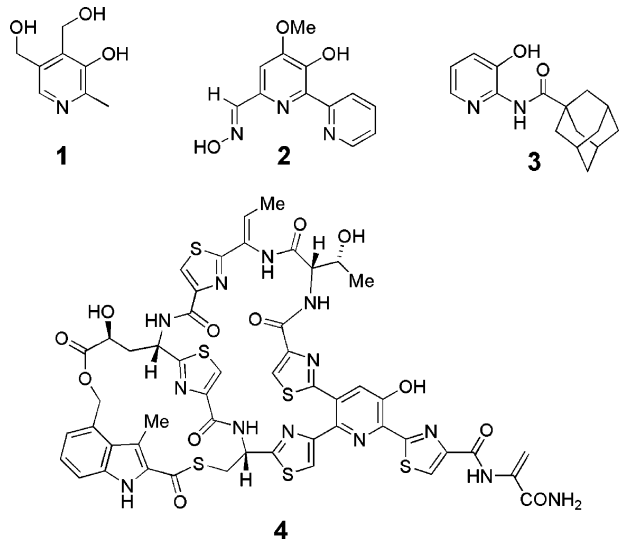


FIGURE 1. Bioactive 3-Hydroxypyridines

3-hydroxypyridines easily adopt a zwitterionic ("betainic") state by an O → N proton transfer from the phenolic hydroxyl function,[1] which confers a considerably polar character.

A deeper exploration and utilization of this interesting heteroaromatic scaffold have been hampered by the lack of flexible synthetic access. Common approaches often necessitate

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(1) Schmidt, A. *Curr. Org. Chem.* **2004**, *8*, 653.
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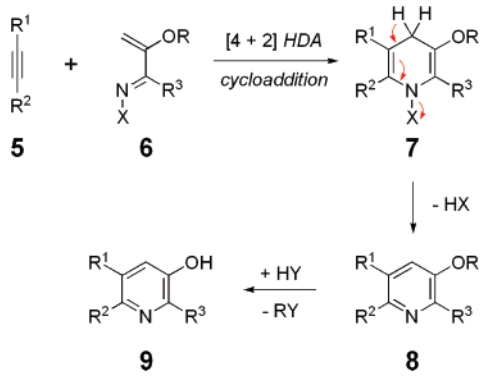
(6) Constantine, K. L.; Mueller, L.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 7284.
(7) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685.

10.1021/jo0703505 CCC: $37.00
Published on Web 04/21/2007

SCHEME 1. Mechanistic Rationale for the Direct Formation of 3-Hydroxypyridines by HDA Cycloaddition

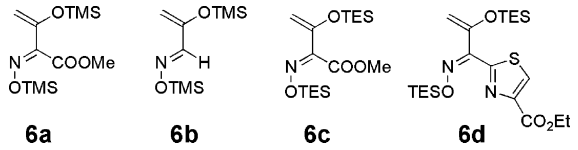


the use of harsh aromatic (re)functionalization reactions of simpler pyridines or of a step-by-step elaboration from 3-hydroxypyridine(s) itself.[8] Within a program that is directed toward a total synthesis of nosiheptide, we give here an account on a general, flexible method to generate 3-hydroxypyridines with diverse substitution patterns.[9,10c]

To address a de novo generation of the 3-hydroxypyridine scaffold, a Diels−Alder (DA) type reaction was envisioned, which is typically the most modular and flexible means for furnishing a six-membered ring.[11] Conceptually, a 3-hydroxypyridine (**9**) could arise from an alkyne (**5**) and a 1-aza diene (**6**) via a [4 + 2] hetero Diels−Alder (HDA) cycloaddition in one operation, if a suitable leaving group X is present on the N1-nitrogen atom to promote aromatization of the expected intermediate dihydropyridine (**7**) (Scheme 1). A 1,4-elimination would then deliver the pyridine (**8**), which would give the free 3-hydroxypyridine (**9**) upon deprotection (Scheme 1).

HDA reactions that follow this general pattern have been studied in some detail, mostly for reactive dienophiles.[12] 1-Azadienes are known to be intrinsically unreactive due to unfavorable orbital coefficients and are prone to tautomerization, but they can be activated and/or stabilized either with electron-donating[13] or electron-withdrawing substituents on the N1-atom.[14] The latter lead into the inverse-electron demand regime and react preferentially with electron-rich alkenes, whereas the former have been applied frequently with electron-poor dienophiles, mostly in the form of *N*,*N*-dialkylhydrazones, which have been pioneered by Ghosez et al.[13]

TABLE 1. 3-Hydroxypyridines 9a−c[a] by HDA Fusion of 1-Azadienes 6 with Limiting Dimethyl Acetylenedicarboxylate (5a)



entry	diene (eq)	conditions	yield	R^3
1	**6a** (1.2)	toluene (0.3 M), 80 °C, 12 h	33% (**9a**)	COOMe
2	**6a** (1.2)	THF (0.6 M), reflux, 20 h	48% (**9a**)	COOMe
3	**6a** (1.2)	CH_3CN (0.6 M), 80 °C, 20 h	48% (**9a**)	COOMe
4	**6a** (1.2)	xylenes (0.4 M), 140°C, 3 h	85% (**9a**)	COOMe
5	**6a** (3.0)	neat, 150 °C, 1 h	99% (**9a**)	COOMe
6	**6b** (3.0)	neat, 150 °C, 3 h	58% (**9b**)	H
7	**6c** (3.0)	neat, 150 °C, 4 h	64% (**9a**)	COOMe
8	**6d** (1.0)	xylenes (0.4 M), 150 °C, 5 h	57% (**9c**)	Thiazolyl

[a] $R^1 = R^2 =$ COOMe.

Consequently, we started to explore hydrazones (**6**, X = NR′R″) initially, but for alkynes, their transformations were hampered by the formation of product mixtures and by incomplete elimination of HX from the putative dihydropyridine intermediate (**7**).[15] We then turned our attention to silylated oximes (**6**, X = $OSiR_3$), which are more easily accessible and should allow the facile deprotection of the hydroxypyridine products (**8**). Literature precedence was limited,[10a,b] but a few six-π-transformations of unsaturated oximes had been documented before in intramolecular cases.[16] The silylated oximes were easily available from β-ketoesters or ketones by α-nitrosation and bis-silylation of the resulting oximes, which delivered the distillable azadienes **6a** (R = TMS, R^3 = COOMe, Table 1) and **6b** (R = TMS, R^3 = H) or the chromatography-stable azadienes **6c** (R = TES, R^3 = COOMe) and **6d** (R = TES, R^3 = 4′-carboxyethyl-1′-thiazolyl), rather straightforwardly.[17]

Initially, dimethyl acetylenedicarboxylate (DMAD, **5a**, $R^1 = R^2$ = COOMe) was found to react smoothly with the silylated oxime enol ether **6a** under neutral conditions. The cycloaddition was only moderately solvent dependent (Table 1, entries 1−4), but high temperatures and high concentrations were found to be beneficial. Neat conditions (in a sealed tube) proved to be optimal and gave the best results (entry **6**). To reach full conversion of the alkyne, an excess of trimethylsilyl (TMS)-derivatized dienes **6a** and **6b** (Table 1) had to be applied to account for their somewhat unstable nature (vide infra). A brief screening of σ- or π-Lewis acids as potential promoters ($LiNTf_2$, MgI_2, Me_2AlCl, $PdCl_2$, and PEt_3AuCl)[18] was not met with success. Nevertheless, both the unsubstituted azadiene **6b** as well as the more complex, thiazole-bearing diene **6d** transformed

(8) Some examples: (a) Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1939**, *61*, 1245. (b) Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C.-g. *Tetrahedron Lett.* **1997**, *38*, 3539. (c) Mongin, F.; Trécourt, F.; Gervais, B.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 3272.

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(11) Selected overviews: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Permagon Press: Oxford, 1991; Vol 5, pp 315−401. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(12) Reviews: (a) Behfourouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259. (b) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.

(13) (a) Serck-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (b) Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. *Synthesis* **1984**, 930. (c) Ghosez, L.; Serck-Poncin, B.; Rivera. M.; Bayard, P.; Sainte, F.; Demoulin, A.; Hesbain-Frisque, A. M.; Mockel, A.; Munoz, L.; Bernard-Henriet, C. *Lect. Heterocycl. Chem.* **1985**, *8*, 69. (d) Potts, K. T.; Walsh, E. B.; Bhattarcharjee, D. *J. Org. Chem.* **1987**, *52*, 2285. (e) Pautet, F.; Nebois, P.; Bouaziz, Z.; Fillion, H. *Heterocycles* **2001**, *54*, 1095.

(14) (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (c) For an organocatalytic variant see He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

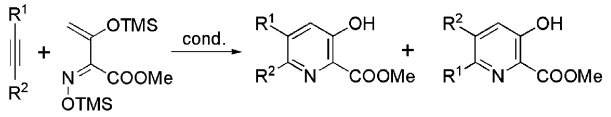
(15) Tautomer formation. Data not shown.

(16) (a) Büchi, G.; Galindo, J. *J. Org. Chem.* **1991**, *56*, 2605. (b) François, D.; Maden, A.; Murray, W. V. *Org. Lett.* **2004**, *6*, 1931.

(17) See supporting information for details.

(18) Reviews: (a) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (b) Kumar, A. *Chem. Rev.* **2001**, *101*, 1.

TABLE 2. 3-Hydroxypyridines from Unsymmetrical Alkynes



5 **6a** **9d-l** **10d-l**

entry	R^1, R^2	time[a]	total yield	ratio **9**:**10**
d	Ph, COOMe	12 h	93%	70:23
e	Ph, C(O)Me	12 h	42%	1:1
f	Thz, C(O)Me	12 h	62%	6:5
g	Thz, C(O)Me	4 h[b]	81%	2:1
h	Br, Ph	4 h	48%	2:1
i	Ph, Cl	2 h	49%	2:1
k	H, Ph	12 h	90%	66:24
l	H, C(O)Me	18 h[c]	38%	>95:5[d]
m	H, C(O)Me	12 h	54%	>95:5[d]
n	H, C(O)Ph	12 h	75%	98:2
o	Ph, Ph	12 h	0%	
p	TMS, H	12 h	0%	
q	C_9H_{19}, H	12 h	0%	

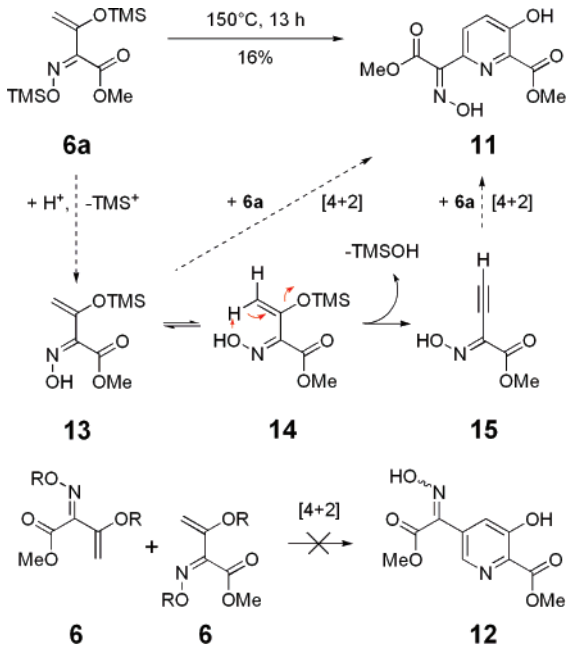
[a] At 150 °C neat, with 3 equiv of **6a**. [b] At 180 °C in xylenes. [c] At 100 °C neat. [d] The minor isomer was not isolated. Thz = 4-carboxymethylthiazolyl (**17**).

well. Increasing the size of the silyl group (TMS → triethylsilyl (TES)) was found to lead to lower reactivity, but the azadienes thus obtained were more stable and easier to handle. Interestingly, when applying TMS- or TES-derivatized 1-azadienes (**6**) to the cycloaddition reaction, no 3-*O*-silyl groups were retained in the isolated products (**9**). This fact reflects the properties of the pronounced leaving group of the betainic 3-hydroxypyridine heterocycle.[1] A close inspection of the crude reaction mixtures by NMR and GC/MS revealed that a considerable portion of the presumed initial product (**8**) suffered a loss of the SiR_3-group under the conditions of the cycloaddition, likely by the attack of nucleophilic components of the reaction mixture (eliminated silanol HX, decomposed 1-azadiene) or by the attack of adventitious water. The remaining TMS/TES groups are lost during workup,[19] which saves a deprotection step.[10c]

DMAD is one of the most reactive alkynes. Therefore, we then turned our attention to more diverse and synthetically more useful alkyne dienophiles (**5**, Table 2). It was pleasing to find out that any alkyne bearing an electron-withdrawing group would participate in good to excellent yields (entries **d**−**n**). The reaction was limited only by volatility (entries **l** and **m**). Monosubstituted aromatic alkynes were also found to react smoothly (entry **k**), but diphenylacetylene and electron-rich alkynes were inert under these conditions (entries **o**−**q**).

In all of the cases examined, the 3-hydroxypridine isomer (**9**) with the more electronegative substituent in the 6-position was favored (Table 2).[20] The 5-isomers (**10**) were formed in minor amounts for the disubstituted alkynes, but they were easily separable by column chromatography in all cases. Higher temperatures and elevated pressure slightly enhanced the regioselectivity (compare entries **f** and **g**). To our delight, the transformation was found to be completely regioselective with two monosubstituted alkynyl ketones (entries **l**−**n**, also vide infra). We were not able to identify any intermediates or side products apart from the apparent decomposition of diene **6a** by two consecutive desilylations (GC-MS) and the small amounts (generally <5%) of the homodimer **11** of the diene **6a** (Scheme 2).

SCHEME 2. Mechanistic Pathways for Homodimer Formation from Diene 6a[a]



[a] R = TMS.

Under forcing conditions, the homodimer **11** was reproducibly formed (Scheme 2) always as a single 6-substituted regioisomer, as was confirmed by extensive 2D-NMR analysis (COSY, HSQC, and HMBC). The regiochemistry and high selectivity is surprising, as presumably the 5-substituted isomer **12** could be formed via a typical DA reaction (Scheme 2, bottom). However, with 2-azadiene homodimers, similar end-to-end fusion DA products have been reported.[21] Interestingly, the TES-activated diene **6c** was found to be completely stable and unreactive to itself under prolonged heat treatment up to 270 °C, which indicated that the bis-silylated 1-azadienes **6** are unlikely to homodimerize under thermal conditions. Given the fact that the TMS-activated diene **6a** is slowly losing TMS groups upon thermal stress (as monitored by TLC and GC-MS), the clean formation of dimer **11** likely involves a desilylated oxime (**13** or **14**), which could directly react further with **6a**. Another possibility would be an intramolecular β-elimination of the enol ether **14** to a terminal alkyne **15**, which might occur under these forced conditions.[22] Alkyne **15** would quickly be captured by the excess of azadiene **6a** present in the mixture to form the apparent homodimer **11** with the same high regiose-

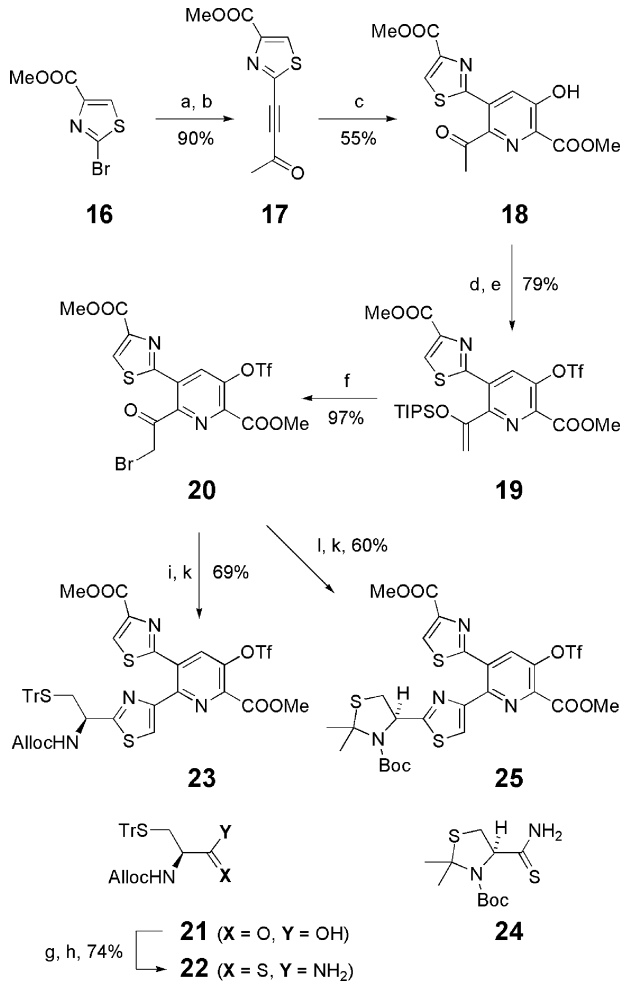
(19) In our hands, both 3-*O*-TMS- and TES-protected 3-hydroxypyridines were unstable to standard aqueous workup conditions as well as standard SiO_2-based purification (TLC and flash column chromatography).

(20) All regioisomers have been unequivocally assigned by means of 2-D NMR data (DQF-COSY, HSQC, HMBC).

(21) (a) Wulff, G.; Böhnke, H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 90. (b) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941. (c) Moody, C. J.; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760.

(22) We have not succeeded in securing proof for the intermediacy of alkyne **15**, but β-eliminations of enol ethers have considerable precedence; see for example (a) Hargrove, R. J.; Stang, P. J. *J. Org. Chem.* **1974**, *39*, 581. (b) Kuwajima, I.; Takeda, R. *Tetrahedron Lett.* **1981**, *22*, 2381. (c) Seyferth, D.; Langer, P.; Döring, M. *Organometallics* **1995**, *14*, 4457. (d) Langer, P.; Döring, M.; Seyferth, D.; Görls, H. *Chem.—Eur. J.* **2001**, *7*, 573.

SCHEME 3. Synthesis of the Nosiheptide Core Structures 23 and 25[a]



[a] (a) 3-butyn-2-ol, 1% $PdCl_2$, 2% CuI, 2% PPh_3, NEt_3, DMF, 80 °C; (b) IBX, THF/DMSO, 0 → 20 °C; (c) **6a** (3 eq.), toluene, 180 °C; (d) Tf_2O, NEt_3, CH_2Cl_2, 0 °C; (e) TIPSOTf, NEt_3, CH_2Cl_2, 0 °C; (f) NBS, THF/H_2O; (g) HOSu, DCC, 0 °C, then NH_4OH; (h) Lawesson's reagent, CH_2Cl_2, r.t.; (i) **22**, $KHCO_3$, THF, −40 °C; (k) TFAA, 2,6-lutidine, −20 °C; (l) **24**, $KHCO_3$, THF, −40 °C.

lectivity observed for the alkynyl ketones. Further experimentation will be necessary to clarify this issue.

All of the data for the alkyne dienophiles above are in line with the notion that a normal-electron demand HDA reaction pathway is operative for these azadiene-alkyne HDA reactions. The regioselectivity would result in each case from a matching HOMO/LUMO pairing of the polarized dienes and dienophiles,[23] with the diene being a 1-aza analogue of Danishefsky's diene.[23b] However, other mechanistic pathways such as a stepwise-polar transformation cannot be unequivocally ruled out at this stage,[24] especially not in case of the side product **11**.

In going further toward a synthesis of nosiheptide (**4**), it was necessary to integrate a thiazole into the alkyne substrate. Along this line bromothiazole **16**[25] was coupled to 3-butyn-2-ol under modified Sonogashira conditions and was subsequently oxidized with IBX to deliver the acetylenic ketone **17** in 90% yield (Scheme 3). The 1-azadiene-HDA pyridine forming reaction was most efficiently carried out, in this case, in an overheated toluene solution (180 °C) to provide ketone **18** (55%) along with its regioisomer **18a** (28%), which was readily separated, also on a multigram scale.

A regioselective thiazole annulation to 3-hydroxypyridine **18** was addressed next via a Hantzsch condensation. To realize a selective α-bromination of the methyl ketone **18**, it was found to be necessary to deactivate the phenolic hydroxyl as a triflate and to activate the ketone as a silylenol ether at the same time (Scheme 3). With a phenolic TIPS protecting group present, the partial bromination of the hydroxypyridine core was difficult to suppress. The resulting silylenol ether **19** (79%) could be cleanly and regioselectively transformed into the bromide **20** (97%), which set the stage for a mild Hantzsch reaction.[26] Toward this end, the essential thioamide **22** was obtained from the suitably protected cysteine derivative **21** in two standard transformations (74%). After careful experimentation it was found that the somewhat sensitive bromide **20** had to be immediately reacted with thioamide **22**. Dehydration with TFAA then proceeded cleanly, and the differentiated nosiheptide core **23** could be obtained in a 69% yield (2 steps). However, after scrutinizing the enantiomeric purity of the product **23** from several runs, it became evident that, in the case of the cysteine derivative **22**, varying degrees of optical purity resulted, especially upon attempted scale up activities. Enantiomeric excess values were determined by trityl-group cleavage and derivatization with (*R*)- and (*S*)-phenylethyl isocyanate, and they revealed an enantiomeric excess (ee) of 60−85%.[17] A solution was found with the ketal-protected thioamide building block **24**.[27] Reaction of **24** with the bromide **22** resulted in the thiazole **25** in excellent yield (60%) over the sequence, and thiazole **25** was found to be of sufficient optical purity after derivatization (>96% ee).[17] Furthermore, conducting the reaction on a larger scale (10 mmol) did not compromise the outcome. The beneficial robustness of the cysteine building block **24** can be tentatively explained by the 5-exo character of the developing *C*2-enol(ate)[28] as well as $A^{1,3}$-strain arguments,[29] which synergistically disfavor a planarized intermediate and help to suppress racemization.

To explore a more convergent synthetic strategy, 1-azadiene **6d** was also combined with alkyne **17**, which furnished the functionalized bis-thiazolo-hydroxypyridine **26** (Scheme 4). However, under a variety of conditions, only minor amounts of the sought cycloaddition product **26** could be isolated, along with a larger number of intractable side products that where extremely difficult to remove. Therefore this route was not investigated further.

(23) (a) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.

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(28) When compared with other α-amino acids, pseudo-prolines (ketal-protected serine, threonine and cysteine derivatives) have, such as proline itself, a much lower tendency to racemize at the α-carbon; for example see Wöhr, T.; Wahl, T.; Nefzi, A.; Rohwedder, B.; Sato, T.; Sun, X. C.; Mutter, M. *J. Am. Chem. Soc.* **1996**, *118*, 9218.

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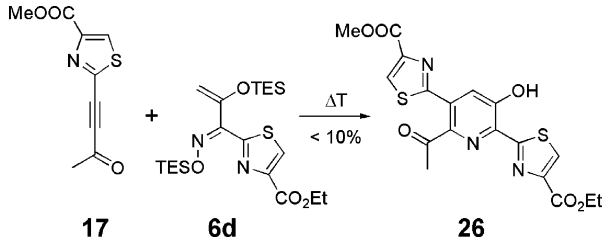
SCHEME 4. Attempted Convergent Synthesis of a Bis-thiazolo-pyridine[a]



[a] Trichlorobenzene, microwave irradiation, 200 °C, 15 min.

In conclusion, we have shown that, in one simple operation from alkynes and silylated enol-oximes, 1-azadiene HDA reactions do provide diverse 3-hydroxypyridines in good yields and selectivities. The choice of diene and dienophile is flexible as long as electronically activated alkynes are employed, and the diene must not be further deactivated by steric bulk. Good to excellent selectivities are obtained from these conditions. Alkynyl ketones were found to deliver the 6-isomer with almost perfect regioselectivity.

This transformation was then utilized to elaborate the fully functionalized core building block **25** for nosiheptide in seven steps from commercial materials, which convincingly demonstrates the power of the 1-azadiene HDA reaction for accessing 3-hydroxypyridines with complex substitution patterns.[30] Importantly, racemization of a cysteine thioamide during the course of a Hantzsch condensation could be suppressed by a judicious choice of protecting groups, and this process could lead to a scaleable synthesis of the important building block **25**. These results will allow for further work toward a total synthesis procedure of nosiheptide (**4**) in the future.

Experimental Section

General Procedure for the Preparation of Compounds 9 and 10. A mixture of alkyne **5** (1 mmol) and 1-aza-1,3-butadiene **6** (1.5−3.0 mmol) was heated to 150 °C under Ar for the time given (TLC control). The reaction mixture was purified by column chromatography on silica gel. Two easily separable isomers each were obtained from alkynes **5d**−**k** as well as **17**.

Trimethyl 3-Hydroxy-2,5,6-pyridinetricarboxylate (9a). Alkyne **5a** (0.12 mL, 1 mmol) yielded 0.269 g (1 mmol, 99%) of **9a** as a colorless solid. mp = 124−126 °C. TLC: R_f = 0.27 (EtOAc/cyclohexane = 1:2). GC-MS (method A): T_R = 4.89 min, *m*/*z* = 269. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.95 (3H, s, $COOCH_3$), 3.96 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 9.67 (1H, s, CH), 11.02 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.19 ($COOCH_3$), 53.25 ($COOCH_3$), 53.69 ($COOCH_3$), 126.98 (C_{Ar}), 130.49 (C_{Ar}), 134.04 (C_{Ar}), 139.91 (C_{Ar}), 159.42 (*C*−OH), 164.89 ($COOCH_3$), 165.34 ($COOCH_3$), 168.82 ($COOCH_3$). IR (KBr): ν = 3155 b, 2846 s, 1728 s, 1657 s, 1555 s, 1505 s, 965 s cm^{-1}. HRMS (FAB), [M + H$^+$], calc: 270.0608, found: 270.0611. Anal. calcd for $C_{11}H_{11}NO_7$: C, 49.08; H, 4.12; N, 5.20; found: C, 49.3; H, 4.0; N, 5.2.

Dimethyl 3-Hydroxypyridine-5,6-dicarboxylate (9b). Alkyne **5a** (0.06 mL, 0.5 mmol) yielded 61 mg (0.29 mmol, 58%) of **9b** as a colorless solid. mp = 133−135 °C. TLC: R_f = 0.12 (EtOAc/light petroleum = 1:1). GC-MS (method A): T_R = 4.85 min, *m*/*z* = 211. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.85 (3H, s, $COOCH_3$), 3.86 (3H, s, $COOCH_3$), 7.47 (1H, d, *J* = 2.7, CH), 8.15 (1H, bs, −OH), 8.32 (1H, d, *J* = 2.5, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 52.93 ($COOCH_3$), 53.06 ($COOCH_3$), 122.89 (C_{Ar}), 130.87 (C_{Ar}), 138.16 (C_{Ar}), 139.39 (C_{Ar}), 155.74 (*C*−OH), 165.48 ($COOCH_3$), 166.83 ($COOCH_3$). IR (KBr): ν = 3100 m, 2954 s, 1644 s, 1605 s, 1504 s, 962 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 212.0553, found: 212.0516. Anal. calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63; found: C, 51.0; H, 4.4; N, 6.4.

Dimethyl 2-(4-(Ethoxycarbonyl)thiazol-2-yl)-3-hydroxypyridine-5,6-dicarboxylate (9c). Alkyne **5a** (0.12 mL, 1 mmol) and 1-aza diene **6d** (0.30 g, 0.64 mmol) in xylenes (1.5 mL) yielded 0.132 g (0.36 mmol, 57%) of **9c** as a yellow, fluorescent solid. mp = 136−138 °C. TLC: R_f = 0.11 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 9.88 min, *m*/*z* = 366. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.41−1.45 (3H, t, *J* = 7.2, CH_2CH_3), 3.95 (3H, s, $COOCH_3$), 3.99 (3H, s, $COOCH_3$), 4.41−4.47 (2H, q, *J* = 7.0, CH_2CH_3), 7.81 (1H, s, CH), 8.30 (1H, s, CH), 11.94 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 14.29 (CH_2CH_3), 53.01 ($COOCH_3$), 53.08 ($COOCH_3$), 61.79 (CH_2CH_3), 126.36 (C_{Ar}), 129.12 (C_{Ar}), 129.51 (C_{Ar}), 135.55 (C_{Ar}), 141.35 (C_{Ar}), 146.74 (C_{Ar}), 153.75 (*C*−OH), 160.18 (C_{Ar}), 165.23 ($COOCH_3$), 165.86 ($COOCH_3$), 168.69(*C*OOEt). IR (KBr): ν = 3402 b, 2960 s, 2922 s, 1741 s, 1726 s, 1568 m, 1221 s, 798 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 367.0594, found: 367.0629.

Dimethyl 3-Hydroxy-5-phenylpyridine-2,6-dicarboxylate (9d). Alkyne **5d** (0.16 g, 1 mmol) yielded 0.2 g (0.7 mmol, 70%) of **9d** as a colorless solid. mp = 111−113 °C. TLC: R_f = 0.15 (EtOAc/cyclohexane = 1:2). GC-MS (method A): T_R = 5.43 min, *m*/*z* = 287. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.63 (3H, s, $COOCH_3$), 4.07 (3H, s, $COOCH_3$), 7.28−7.44 (5H, m, Ar), 8.60 (1H, s, CH), 11.07 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 52.41 ($COOCH_3$), 53.47 ($COOCH_3$), 128.04 (Ar), 128.61 (Ar), 128.68 (Ar), 131.21 (*C*−COOMe), 132.02 (*C*−COOMe), 132.62(Ar), 139.41(*C*−Ar), 140.89 (*C*H), 156.27 (*C*−OH), 165.96 ($COOCH_3$), 169.61 ($COOCH_3$). IR (KBr): ν = 3179 b, 2957 m, 2919 m, 2850 m, 1747 s, 1685 s, 1448 s, 807 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 288.0866, found: 288.0906.

Dimethyl 3-Hydroxy-6-phenylpyridine-2,5-dicarboxylate (10d). Alkyne **5d** (0.16 g, 1 mmol) yielded 66 mg (0.23 mmol, 23%) **of 10d** as a colorless solid. mp = 108−109 °C. TLC: R_f = 0.37 (EtOAc/cyclohexane = 1:2). GC-MS (method A): T_R = 5.38 min, *m*/*z* = 287. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.71 (3H, s, $COOCH_3$), 4.06 (3H, s, $COOCH_3$), 7.40−7.50 (5H, m, Ar), 7.72 (1H, s, CH), 10.69 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 52.69 ($COOCH_3$), 53.37 ($COOCH_3$), 127.67(*C*H), 128.29 (Ar), 128.41 (Ar), 128.61 (Ar), 130.66 (*C*−COOMe), 132.77 (Ar), 138.86 (*C*−COOMe), 149.86 (*C*-Ar), 156.90 (*C*-OH), 167.25 ($COOCH_3$), 169.48 ($COOCH_3$). IR (KBr): ν = 3225 b, 3023 m, 2957 m, 1730 s, 1687 s, 1455 s, 798 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 288.0866, found: 288.0845. Anal. calcd for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88; found: C, 62.8; H, 4.9; N, 4.5.

Methyl 6-Acetyl-3-hydroxy-5-phenylpyridine-2-carboxylate (9e). Alkyne **5e** (0.5 g, 3.47 mmol) yielded 0.194 g (0.72 mmol, 21%) of **9e** as a colorless solid. mp = 136−138 °C. TLC: R_f = 0.24 (EtOAc/light petroleum = 1:1). GC-MS (method B): T_R = 8.29 min, *m*/*z* = 271. ^{1}H NMR (400 MHz, CD_3CN) δ = 1.99 (3H, s, CH_3), 4.01 (3H, s, $COOCH_3$), 7.33−7.49 (5H, m, Ar), 8.31 (1H, s, CH), 11.04 (1H, s, OH). ^{13}C NMR (100.6 MHz, CD_3CN) δ = 30.43 (CH_3), 53.62 ($COOCH_3$), 129.15 (C_{Ar}), 129.62 (C_{Ar}), 130.25 (C_{Ar}), 131.89 (C_{Ar}), 133.53 (C_{Ar}), 137.02 (C_{Ar}), 139.61 (C_{Ar}), 141.37 (C_{Ar}), 156.55 (*C*−OH), 170.61 ($COOCH_3$), 201.90 (*C*(O)CH_3). IR (KBr): ν = 3037 s, 2967 s, 1746 s, 1696 s, 1678 s, 1397 s, 1178 s, 818 s, 747 s cm^{-1}. HRMS (ESI), [M + H$^+$], calcd: 272.0917, found: 272.0918.

Methyl 5-Acetyl-3-hydroxy-6-phenylpyridine-2-carboxylate (10e). Alkyne **5e** (0.5 g, 3.47 mmol) yielded 0.198 g (0.73 mmol, 21%) of **10e** as a light yellow solid. mp = 101−103 °C. TLC: R_f = 0.41 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 8.19 min, *m*/*z* = 271. ^{1}H NMR (400 MHz, CD_3CN) δ = 2.21 (3H, s, CH_3), 3.99 (3H, s, $COOCH_3$), 7.44 (5H, s, Ar), 7.51 (1H, s, CH),

(30) A different approach to the nosiheptide core structure has been detailed. (a) Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C. G. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1391. (b) See also ref 8b.

10.56 (1H, s, OH). ^{13}C NMR (100.6 MHz, CD_3CN) δ = 30.44 (*C*H$_3$), 53.76 (COO*C*H$_3$), 126.13 (*C*H), 129.35 (Ar), 129.61 (Ar), 129.63 (Ar), 131.33 (*C*-COOMe), 139.75 (Ar), 142.32 (*C*−CH), 148.86 (*C*-Ar), 157.73 (*C*−OH), 170.25 (*C*OOCH$_3$), 202.54 (*C*(O)-CH$_3$). IR (KBr): ν = 2899 s, 2899 w, 2850 w, 1744 s, 1697 s, 1201 s, 849 s, 809 s cm^{-1}. HRMS (ESI), [M + H$^+$], calcd: 272.0917, found: 272.0918.

Methyl 5-Bromo-3-hydroxy-6-phenylpyridine-2-carboxylate (9h). Alkyne **5h** (90 mg, 0.497 mmol) yielded 49 mg (0.16 mmol, 32%) of **9h** as a colorless solid. mp = 103−104 °C. TLC: R_f = 0.30 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.53 min, *m*/*z* = 307, 308. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.03 (3H, s, COOCH$_3$), 7.42−7.63 (5H, m, Ar), 7.75 (1H, s, CH), 10.69 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.28 (COO*C*H$_3$), 125.69(*C*−Br), 128.03 (Ar), 128.73 (Ar), 129.48 (Ar), 130.80 (Ar), 136.46 (*C*H), 138.51 (*C*-COOMe), 150.36 (*C*−Ar), 157.23 (*C*-OH), 169.74 (*C*OOCH$_3$). IR (KBr): ν = 3171 b, 2957 m, 1683 s, 1504 m, 1434 s, 1207 s, 801 s cm^{-1}. HRMS (FAB), [M$^+$], calcd: 306.9844, found: 306.9843 [^{79}Br]. Anal. calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; N, 4.55; found: C, 50.8; H, 3.6; N, 4.2.

Methyl 6-Bromo-3-hydroxy-5-phenylpyridine-2-carboxylate (10h). Alkyne **5h** (90 mg, 0.497 mmol) yielded 25 mg (0.08 mmol, 16%) of **10h** as a colorless solid. mp = 100−101 °C. TLC: R_f = 0.19 (EtOAc/cyclohexane = 1:2). GC-MS (method A): T_R = 5.31 min, *m*/*z* = 307, 308. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.07 (3H, s, COOCH$_3$), 7.33−7.51 (5H, m, Ar), 8.48 (1H, s, CH), 11.07 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.44 (COO*C*H$_3$), 127.63 (C$_{Ar}$), 128.38 (C$_{Ar}$), 128.61 (C$_{Ar}$), 128.95 (C$_{Ar}$), 129.20 (C$_{Ar}$), 133.34 (C$_{Ar}$), 139.99 (C$_{Ar}$), 143.37 (C$_{Ar}$), 157.00 (*C*−OH), 169.96 (*C*OOCH$_3$). IR (KBr): ν = 3128 b, 1746 s, 1681 s, 1504 s, 1360 s, 898 s, 811 s cm^{-1}. HRMS (FAB), [M$^+$], calc: 306.9844, found: 306.9882 [^{79}Br].

Methyl 6-Chloro-3-hydroxy-5-phenylpyridine-2-carboxylate (9i). Alkyne **5i** (70 mg, 0.51 mmol) yielded 46 mg (0.17 mmol, 34%) of **9i** as a colorless solid. mp = 108−109 °C. TLC: R_f = 0.28 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.32 min, *m*/*z* = 263. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 (3H, s, COOCH$_3$), 7.36−7.51 (5H, m, Ar), 8.36 (1H, s, CH), 11.11 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.41 (COO*C*H$_3$), 128.24 (*C*−Cl), 128.35 (Ar), 128.99 (Ar), 129.45 (Ar), 131.34 (Ar), 136.27 (*C*−COOMe), 137.71 (*C*-Ar), 141.19 (*C*H), 157.06 (*C*−OH), 169.85 (*C*OOCH$_3$). IR (KBr): ν = 3054 b, 2923 m, 1673 s, 1576 m, 1397 s, 913 s, 812 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 264.0422, found: 264.0437.

Methyl 5-Chloro-3-hydroxy-6-phenylpyridine-2-carboxylate (10i). Alkyne **5i** (70 mg, 0.51 mmol) yielded 20 mg (0.08 mmol, 15%) of **10i** as a colorless solid. mp = 164−165 °C. TLC: R_f = 0.46 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.30 min, *m*/*z* = 263. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.04 (3H, s, COOCH$_3$), 7.42−7.67 (5H, m, Ar), 7.54 (1H, s, CH), 10.72 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.25 (COO*C*H$_3$), 126.61 (C$_{Ar}$), 127.38 (C$_{Ar}$), 128.06 (C$_{Ar}$), 128.12 (C$_{Ar}$), 128.78 (C$_{Ar}$), 129.44 (C$_{Ar}$), 135.81 (C$_{Ar}$), 137.20 (C$_{Ar}$), 157.56 (*C*−OH), 169.59 (*C*OOCH$_3$). IR (KBr): ν = 3157 s, 2902 m, 1683 s, 1556 m, 1436 s, 802 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 264.0422, found: 264.0445.

Methyl 3-Hydroxy-6-phenylpyridine-2-carboxylate (9k). Alkyne **5k** (0.11 mL, 1 mmol) yielded 0.15 g (0.66 mmol, 66%) of **9k** as a colorless solid. mp = 107−109 °C. TLC: R_f = 0.47 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.13 min, *m*/*z* = 229. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.07 (3H, s, COOCH$_3$), 7.36−7.39 (1H, m, Ar), 7.40, 7.425 (1H, d, *J* = 8.8, CH), 7.43−7.47 (2H, m, Ar), 7.82, 7.84 (1H, d, *J* = 8.8, CH), 7.92−7.94 (2H, m, Ar), 10.71 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.03 (COO*C*H$_3$), 126.57 (C$_{Ar}$), 126.84 (C$_{Ar}$), 126.94 (C$_{Ar}$), 128.68 (C$_{Ar}$), 128.79 (C$_{Ar}$), 129.36 (C$_{Ar}$), 138.31 (C$_{Ar}$), 149.48 (C$_{Ar}$), 157.80 (*C*−OH), 170.16 (*C*OOCH$_3$). IR (KBr): ν = 3092 b, 2955 m, 1714 s, 1694 s, 1372 s, 805 s cm^{-1}. HRMS (ESI), [M + H$^+$], calcd: 230.0812, found: 230.0811.

Methyl 3-Hydroxy-5-phenylpyridine-2-carboxylate (10k). Alkyne **5k** (0.11 mL, 1 mmol) yielded 55 mg (0.24 mmol, 24%) of **10k** as a colorless solid. mp = 83−86 °C. TLC: R_f = 0.13 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.16 min, *m*/*z* = 229. ^{1}H NMR (400 MHz, CD_3CN) δ = 4.00 (3H, s, COOCH$_3$), 7.44−7.51 (3H, m, Ar), 7.53, 7.54 (1H, d, *J* = 4.6, CH), 7.64−7.66(2H, m, Ar), 8.26, 8.27 (1H, d, *J* = 4.6, CH), 11.18 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 53.65 (COO*C*H$_3$), 129.32 (C$_{Ar}$), 129.62 (C$_{Ar}$), 130.07 (C$_{Ar}$), 130.39 (C$_{Ar}$), 131.51 (C$_{Ar}$), 135.76 (C$_{Ar}$), 138.89 (C$_{Ar}$), 142.14 (C$_{Ar}$), 157.00 (*C*−OH), 171.57 (*C*OOCH$_3$). IR (KBr): ν = 2955 w, 2921 s, 2852 s, 1744 s, 1694 s, 1245 s, 863 s, 807 s cm^{-1}. HRMS (ESI), [M + H$^+$], calcd: 230.0812, found: 230.0810.

Methyl 6-Acetyl-3-hydroxypyridine-2-carboxylate (9m). Alkyne **5m** (0.156 mL, 2 mmol) yielded 0.21 g (1.07 mmol, 54%) of **9m** as a colorless solid. mp = 120−122 °C. TLC: R_f = 0.35 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 6.30 min, *m*/*z* = 195. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.71 (3H, s, COCH$_3$), 4.08 (3H, s, COOCH$_3$), 7.43, 7.45 (1H, d, *J* = 8.8, C*H*CHCOH), 8.18, 8.2 (1H, d, *J* = 8.8, CHC*H*COH), 11.11 (1H, s, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 25.16 (C(O)*C*H$_3$), 53.26 (COO*C*H$_3$), 126.58 (*C*H), 127.95 (C*C*HCHCOH), 128.64 (*C*COOMe), 145.97 (*CC*(O)Me), 161.3 (*C*−OH), 169.68 (*C*OOMe), 198.2 (*C*(O)Me). IR (KBr): ν = 3192 b, 2968 m, 2925 m, 2855 m, 1699 s, 1681 s, 1574 s, 851 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 196.0604, found: 196.0587. Minor isomer **10m**: GC-MS (method B): T_R = 6.55 min, 195 (M$^+$)

Methyl 6-Benzoyl-3-hydroxypyridine-2-carboxylate (9n). Alkyne **5n** (0.25 g, 1.92 mmol) yielded 0.365 g (1.42 mmol, 74%) of **9n** as a light yellow solid. mp = 94−96 °C. TLC: R_f = 0.38 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 8.09 min, *m*/*z* = 257. ^{1}H NMR (400 MHz, CD_3CN) δ = 3.92 (3H, s, COOMe), 7.43−7.48 (2H, m, Ar), 7.46, 7.49 (1H, d, *J* = 8.8, CH), 7.56−7.61 (1H, m, Ar), 8.05−8.07 (2H, m, Ar), 8.11,8.13 (1H, d, *J* = 8.8, CH), 10.93 (1H, s, OH). ^{13}C NMR (100.6 MHz, CD_3CN) δ = 53.58 (COO*C*H$_3$), 127.33 (*C*H), 128.70 (Ar), 129.25 (*C*−COOMe), 131.20 (*C*H), 131.64 (Ar), 133.41 (Ar), 137.10 (Ar), 147.09 (*C*−C(O)Ar), 160.91 (*C*−OH), 170.23 (*C*OOMe), 191.79 (*C*(O)−Ar). IR (KBr): ν = 3067 s, 2916 w, 1679 s, 1577 s, 1219 s, 944 s, 698 s cm^{-1}. HRMS (ESI), [M + H$^+$], calcd: 258.0761, found: 258.0762. Minor isomer **10n** (9 mg, 1% as determined by ^{1}H NMR), GC-MS (method B): T_R = 8.28 min, *m*/*z* = 257.

Thiazolylalcohol (27). In a dry Schlenk flask, $PdCl_2$ (10 mg, 0.059 mmol), PPh_3 (30.9 mg, 0.118 mmol), and CuI (22 mg, 0.118 mmol) were dissolved in DMF (15 mL) under argon, and the mixture was stirred for 30 min. Bromothiazole **16** (1.3 g, 5.9 mmol), 3-butyn-2-ol (0.64 mL, 8.8 mmol), and triethylamine (1.6 mL, 11.8 mmol) were added to the mixture. The mixture was heated to 80 °C for 2 h (TLC control), and it turned dark brown. The mixture was cooled to room temperature, diluted with dichloromethane (50 mL), and filtered through Celite. The pad of Celite was rinsed with dichloromethane (3 × 10 mL), and the combined filtrates were concentrated and purified by column chromatography on silica gel (EtOAc/cyclohexane = 1:4) to give 0.90 g (4.3 mmol, 90%) of thiazolylalcohol **27** as a colorless solid. mp = 94−95 °C. TLC: R_f = 0.15 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 7.22 min, *m*/*z* = 211. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.56 (3H, d, *J* = 6.7, CH$_3$), 2.23 (1H, s, OH), 3.95 (3H, s, COOCH$_3$), 4.77 (1H, q, *J* = 6.5, CHCH$_3$), 8.17 (1H, s, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 23.61 (CH*C*H$_3$), 52.48 (*C*H$_3$), 58.59 (*C*HCH$_3$), 76.44 (C−*C*COH), 96.89 (C*C*OH), 128.64 (*C*H), 147.16 (*C*−CCOH), 148.76 (*C*−COOCH$_3$), 161.22 (*C*OOCH$_3$). IR (KBr): ν = 3343 b, 2981 s, 2486 s, 2230 s, 1681 s, 1248 s, 928 s, 771 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 212.0376, found: 212.0416.

Methyl 2-But-1′-yne-3′-oxo-4-thiazolecarboxylate (17). A mixture of IBX (1.57 g, 5.59 mmol) in dry DMSO (10 mL) was added dropwise to a cooled solution (0 °C) of thiazolylalcohol **27** (0.9 g, 4.3 mmol) in dry THF (10 mL) under argon. The solution was allowed to warm to room temperature after 2 h and was stirred for

12 h (TLC control). The mixture was diluted with water (60 mL) and was extracted with diethyl ether (4 × 50 mL). The combined extracts were dried with sodium sulfate and were evaporated to dryness. Purification by column chromatography on silica gel (EtOAc/cyclohexane = 1:6) gave 0.89 g (4.26 mmol, 99%) of thiazolylketone **17** as a colorless solid. mp = 159−160 °C. TLC: R_f = 0.39 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 6.99 min, *m*/*z* = 209. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.44 (3H, s, C(O)CH_3), 3.94 (3H, s, COOCH_3), 8.32 (1H, s, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 32.44 (C(O)*C*H$_3$), 52.70 (*C*H$_3$), 79.52 (C−*C*CC(O)CH$_3$), 90.44 (*C*C(O)CH$_3$), 130.89 (*C*H), 146.21 (*C*−CC(O)CH$_3$), 148.17 (*C*−COOCH$_3$), 160.71 (*C*OOCH$_3$), 183.06 (*C*(O)CH$_3$). IR (KBr): ν = 3078 s, 2204 s, 1728 s, 1673 m, 1453 s, 1231 s, 861 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 210.0219, found: 210.0219. Anal. calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.69; found: C, 51.7; H, 3.5; N, 6.8.

Methyl 5-(4-(Methoxycarbonyl)thiazol-2-yl)-6-acetyl-3-hydroxypyridine-2-carboxylate (18). A solution of thiazolylketone **17** (1.0 g, 4.78 mmol) and 2-methoxycarbonyl-1,3-bis(trimethylsiloxy)-1-aza-1,3-butadiene (4.15 g, 14.4 mmol) in toluene (1 mL) was heated to 180 °C for 3 h under Ar (CAUTION! Use a thick-walled sealed tube!). After the solution was cooled to room temperature, the reaction mixture was purified by column chromatography on silica gel (EtOAc/light petroleum = 1:4) to give 888 mg (2.64 mmol, 55%) of ketone **18** and 447 mg (1.33 mmol, 28%) of its 5-acetyl regioisomer **18a** as colorless solids.

Ketone 18: mp = 217 °C (decomp.). TLC: R_f = 0.06 (EtOAc/cyclohexane = 1:2). GC-MS (method B): T_R = 9.51 min, *m*/*z* = 336. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.70 (3H, s, C(O)CH_3), 3.95 (3H, s, COOCH_3), 4.09 (3H, s, COOCH_3), 7.68 (1H, s, CH), 8.34 (1H, s, CH), 11.02 (1H, s, C−OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 27.44 (C(O)*C*H$_3$), 52.52 (COO*C*H$_3$), 53.44 (COO*C*H$_3$), 129.00 (*C*H), 129.09 (*C*−COOMe), 129.69 (*C*H), 134.34 (*C*−CH), 145.02 (*C*−C(O)Me), 147.11 (*C*−COOMe), 159.37 (*C*−OH), 161.55 (*C*OOMe), 163.32 (C−*C*(N)S), 169.08 (*C*OOMe), 198.79 (*C*(O)CH$_3$). IR (KBr): ν = 3157 s, 2914 s, 2854 s, 1729 m, 1692 m, 1461 s, 1377 s, 1179 w, 890 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 337.0489, found: 337.0515.

Ketone Isomer 18a: mp = 186 °C (decomp.). R_f = 0.17 (minor isomer). GC-MS (method B): T_R = 9.41 min, *m*/*z* = 336. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.64 (3H, s, C(O)CH_3), 3.93 (3H, s, COOCH_3), 4.09 (3H, s, COOCH_3), 7.29 (1H, s, CH), 8.22 (1H, s, CH), 10.91 (1H, s, C−OH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 30.91 (C(O)*C*H$_3$), 52.37 (COO*C*H$_3$), 53.44 (COO*C*H$_3$), 124.36 (*C*H), 129.36 (*C*H), 129.52 (*C*−COOMe), 138.08 (*C*−C(N)S), 142.32 (*C*−C(O)Me), 147.57 (*C*-COOMe), 159.12 (*C*−OH), 161.58 (*C*OOMe), 166.51 (*C*(N)S), 168.85 (*C*OOMe), 201.03 (*C*(O)CH$_3$). IR (KBr): ν = 3124 s, 2958 w, 2922 w, 2852 w, 1743 s, 1704 s, 1454 s, 1216 s, 808 s, 762 s cm^{-1}. HRMS (ESI), [M + H$^+$], calc: 337.0489, found: 337.0492.

Methyl 5-(4-Methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-6-(1-triisopropylsilyloxy-vinyl)-pyridine-2-carboxylate (19). Trifluoromethanesulfonic anhydride (0.9 mL, 5.4 mmol) was added dropwise over 10 min to a solution of hydroxypyridine **18** (1.2 g, 3.6 mmol) and triethylamine (1 mL, 7.2 mmol) in dry dichloromethane (40 mL) at 0 °C under an Ar atmosphere. The reaction mixture was gradually warmed to room temperature and was stirred for 12 h. The reaction was quenched by the addition of phosphate buffer (pH 2, 0.50 M, 20 mL), and the solution was extracted with dichloromethane (3 × 50 mL), dried with Na_2SO_4, and concentrated. Purification by column chromatography on silica gel (EtOAc/light petroleum = 1:3) gave 0.81 g (1.7 mmol, 80% based on recovered starting material) of pyridineketone **28** as a colorless solid. mp = 126−128 °C. TLC: R_f = 0.22 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78 (3H, s, C(O)CH_3), 3.96 (3H, s, COOCH_3), 4.06 (3H, s, COOCH_3), 8.20 (1H, s, CH), 8.38 (1H, s, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 28.10 (C(O)*C*H$_3$), 52.61 (COO*C*H$_3$), 53.46 (COO*C*H$_3$), 116.94, 120.12 (Tf), 130.56 (*C*−C(N)S), 132.40 (*C*H), 133.94 (*C*H), 141.03 (*C*−COOMe), 145.98 (*C*−C(O)Me), 147.74 (*C*-COOMe), 151.91 (*C*-OTf), 160.59 (C−*C*(N)S), 161.21 (*C*OOMe), 161.91 (*C*OOMe),-198.88 (*C*(O)CH$_3$). IR (KBr): ν = 3100 s, 1740 s, 1716 s, 1423 s, 1221 s, 930 s, 893 s, 798 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 468.9982, found: 468.9959.

Triisopropylsilyl triflate (0.68 mL, 2.52 mmol) was added dropwise to a stirring solution of ketone **28** (0.59 g, 1.26 mmol) and triethylamine (0.3 mL, 5.0 mmol) in dry dichloromethane (10 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature after 1 h and was stirred for 12 h. A saturated NaCl solution (20 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried with Na_2SO_4, concentrated to dryness, and purified by column chromatography on silica gel (EtOAc/cyclohexane = 1:12) to give 0.785 g (1.25 mmol, 99%) of enol ether **19** as a yellow oil. TLC: R_f = 0.84 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.87−1.03 (21H, m, TIPS), 3.98 (3H, s, COOCH_3), 4.01 (3H, s, COOCH_3), 4.82, 4.86 (1H, d, *J* = 13.7, C=*CH*$_2$), 5.07, 5.11 (1H, d, *J* = 18.8, C=*CH*$_2$), 8.27 (1H, s, CH), 8.36 (1H, s, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 12.40, 17.67, 52.56, 53.18, 100.44, 130.44, 130.52, 131.34, 132.63, 141.02, 144.50, 147.16, 153.42, 154.19, 161.42, 162.1, 162.51. IR (KBr): ν = 2942 w, 2857 w, 1741 s, 1695 s, 1434 s, 1223 b, 858 s, 799 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 625.1316, found: 625.1291.

Methyl 6-(2-Bromo-acetyl)-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylate (20). NBS (0.23 g, 1.3 mmol) was added at room temperature to a solution of enol ether **19** (0.666 g, 1.1 mmol) in THF/0.5 M phosphate buffer (6:1, 14 mL, pH 7), and the reaction mixture was stirred for 30 min (TLC control). The reaction mixture was diluted with phosphate buffer (pH 7, 20 mL) and was extracted with dichloromethane (3 × 20 mL). The combined extracts were dried with Na_2SO_4, concentrated, and purified by column chromatography on silica gel (diethyl ether/*N*-pentane = 1:3) to yield 0.583 g (1.07 mmol, 97%) of bromoketone **20** as a colorless solid. mp = 133 °C (decomp). TLC: R_f = 0.39 (EtOAc/cyclohexane = 2:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.99 (3H, s, COOCH_3), 4.08 (3H, s, COOCH_3), 4.81 (2H, s, CH_2Br), 8.31 (1H, s, CH), 8.40 (1H, s, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 33.14, 52.71, 53.60, 127.79, 130.76, 133.59, 134.05, 146.51, 148.01, 149.38, 156.04, 159.79, 161.15, 161.64, 191.15. IR (KBr): ν = 2924 s, 2854 s, 1740 b, 1434 s, 1222 s, 800 s cm^{-1}. HRMS (FAB), [M + H$^+$], calcd: 546.9087, found: 546.9122 [^{79}Br].

Methyl 6-[2-(1′-allyoxycarbonylamino-2′-tritylsulfanyl-ethyl)-Thiazol-4-yl]-5-(4-methoxycarbonyl-thiazol-2-yl)-3-trifluoromethanesulfonyloxy-pyridine-2-carboxylate (23). A suspension of thioamide **22** (0.67 g, 1.5 mmol) and anhydrous $KHCO_3$ (0.29 g, 2.9 mmol) in THF (10 mL) was cooled to −40 °C, and bromoketone **20** (0.51 g, 0.93 mmol) in THF (2 mL) was added dropwise. After the mixture was stirred for 2 h, it was allowed to warm to room temperature and was stirred for 48 h. The reaction mixture was filtered under argon and was cooled to −20 °C. 2,6-Lutidine (1.2 mL, 10.5 mmol) and trifluoroacetic anhydride (0.6 mL, 4.4 mmol) were slowly added, and the solution was allowed to stir for 2 h. Brine (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried with Na_2SO_4. Column chromatography (silica gel, EtOAc/light petroleum = 1:5) gave 0.59 g (0.65 mmol, 69%) of thiazolylpyridine **23** as a yellow, microcrystalline solid. mp = 104 °C (decomp.). TLC: R_f = 0.33 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.64−2.86 (2H, m, CH_2CH), 4.02 (3H, s, COOCH_3), 4.11 (3H, s, COOCH_3), 4.57, 4.58 (2H, d, *J* = 5.6, COO*C*H$_2$CH=CH$_2$), 4.73 (1H, m. CH$_2$*C*H), 5.13 (1H, m, NH), 5.28, 5.30 (1H, d, *J* = 10.0, CH=*CH*$_2$), 5.34, 5.38 (1H, d, *J* = 16.8, CH=*CH*$_2$), 5.95 (1H, m, *C*H=CH$_2$), 7.28−7.42 (15H, m, trityl), 7.98 (1H, s, CH), 8.15 (1H, s, CH), 8.34 (1H, s, C*H*=CNCOOMe). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 36.77, 52.03, 52.58, 53.41, 65.97, 67.51, 117.95, 120.19, 123.24, 126.97,

128.09, 129.50, 130.35, 132.25, 132.48, 133.46, 141.62, 144.27, 144.51, 146.95, 150.15, 151.15, 155.01, 161.38, 162.39, 162.45, 171.10. IR (KBr): ν = 2924 s, 2854 s,1731 s, 1494 m, 1433 s, 1217 s, 886 s, 796 s cm^{-1}. $[\alpha]_D^{20} = -2.1$ (c = 1, $CHCl_3$). HRMS (FAB), [M + H$^+$], calcd: 911.1155, found: 911.1165.

Ketal-Protected Building Block (25). A suspension of thioamide **24** (2.45 g, 8.9 mmol) and anhydrous $KHCO_3$ (2.4 g, 24 mmol) in THF 100 mL was cooled to −40 °C, and bromoketone **20** (3.2 g, 5.9 mmol) in THF (20 mL) was added dropwise to the suspension. After the mixture was stirred for 2 h, it was allowed to warm to room temperature and was stirred for 48 h. The reaction mixture was filtered under argon and was cooled to −20 °C. 2,6-Lutidine (7.2 mL, 61.9 mmol) and trifluoroacetic anhydride (4.1 mL, 29 mmol) were slowly added, and the solution was allowed to stir for 2 h. Brine (100 mL) was slowly added, and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried with Na_2SO_4. Column chromatography (silica gel, EtOAc/cyclohexane = 1:5) gave 2.56 g (3.54 mmol, 60%) of thiazolylpyridine **25** as a yellow microcrystalline solid. mp = 108 °C (decomp.). TLC: R_f = 0.35 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (400 MHz, CD_3CN) δ = 1.33 (9H, s, $C(CH_3)_3$), 1.78 (3H, s, CH_3), 1.87 (3H, s, CH_3), 2.77, 2.8 (1H, q, J = 12.3, CH_2), 3.39, 3.40, 3.42, 3.43 (1H, q, J = 5.9, CH_2), 3.88 (3H, s, COOMe), 4.01 (3H, s, COOMe), 5.47 (1H, br, CH), 7.94 (1H, s, CH), 8.30 (1H, s, CCHS), 8.37 (1H, s, CCHS). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 28.41, 29.04, 29.18, 52.85, 53.94, 60.13, 66.08, 108.46, 121.15, 123.76, 131.96, 133.48, 134.13, 142.22, 145.48, 147.76, 151.65, 162.21, 163.54. IR (KBr): ν = 2979 s, 2928 s, 1702 s, 1602 s, 1432 s, 1347 s, 1217 s, 859 s, 798 s cm^{-1}. $[\alpha]_D^{20} = -48.0$ (c = 1, $CHCl_3$). HRMS (FAB), [M + H$^+$], calcd: 725.0686, found: 725.0712.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank the Bayer HealthCare AG, Wuppertal (D), for a donation of equipment. H.-D.A. acknowledges an Emmy−Noether fellowship, and J.-Y. is a member of the International Max−Planck Research School for Chemical Biology.

Supporting Information Available: Additional experimental methods, characterization data, and ^{1}H spectra for compounds **6**−**25**. This material is available free of charge on the Internet at http://pubs.acs.org.

JO0703505