Applications of Crotyldiisopinocampheylboranes in Synthesis: The Total Synthesis of Nikkomycin B

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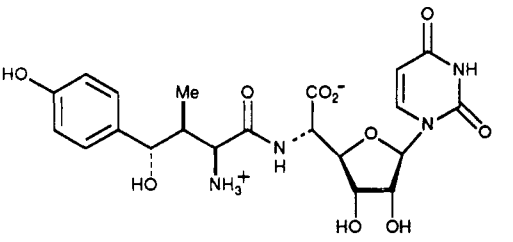
(–)-(*E*)-Crotyldiisopinocampheylborane was employed in a highly diastereoselective and enantioselective synthesis of the γ-hydroxy-β-methyl-α-aminobutanoic acid moiety of nikkomycin B. A protected derivative of this N-terminal amino acid residue was condensed with uracil polyoxin C benzyl ester to provide, on deprotection, the antifungal agent nikkomycin B.

Introduction

The nikkomycins[1] and neopolyoxins[2] are a group of nucleoside di- and tripeptide antibiotics produced by *Streptomyces tendae* and *S. cacaoi* ssp. *asoensis*. Representative examples of these unique natural products include nikkomycin B (**1**), nikkomycin B_x (**2**), and nikkomycin J (**3**). These compounds are potent chitin synthetase inhibitors and they exhibit fungicidal, insecticidal, and acaricidal activities.[1-3] The inhibition of *Botrytis cinerea*, *Pyricularia oryzae*, and *Candida albicans* by the neopolyoxins are particularly noteworthy.[2] The effectiveness of both the nikkomycins and neoployoxins against the medically important pathogen *C. albicans* is significant especially since this opportunistic organism is a major problem with AIDS victims. In consequence of these biological effects, the nikkomycins and neopolyoxins are attractive targets for synthesis.

In 1980, König reported the first synthetic studies in the area by carrying out a nonstereoselective synthesis of the N-terminal amino acid residue of both nikkomycins B (**1**) and B_x (**2**).[1b] The process, which involved a nitrile oxide cycloaddition reaction, is summarized in Scheme I. Thus reaction between alkene **4** and the nitrile oxide derived from the hydroximoyl chloride **5** gave both isoxazolines **6** and **7** (93:7). Ester saponification and isoxazoline reduction gave amino acid **8** as a mixture of racemic C-2 diastereoisomers. Subsequently, König and co-workers refined this chemistry and prepared several optically pure nikkomycin N-terminal amino acids via the resolution of isoxazoline intermediates, the subsequent isoxazoline reduction, and the separation of the C-2 diastereoisomers.[1e,4]



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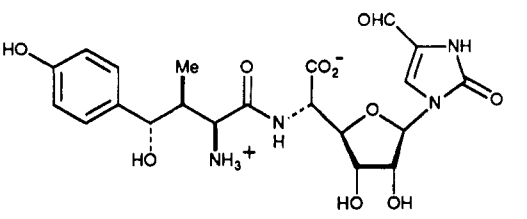

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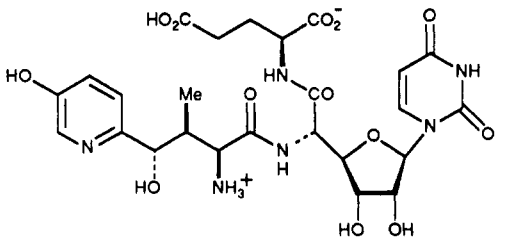


3

In 1987, the Hamburg group applied these methods for the partial synthesis of nikkomycin B_x (**2**) and several analogues.[5] The peptide coupling strategy employed is illustrated by the reaction of the activated ester **9** with the nucleoside **10** (Scheme II). Jäger and co-workers have also employed nitrile oxide cycloaddition chemistry in the synthesis of the N-terminal amino acid unit of nikkomycin B (**1**).[6] This group observed that the lactone **11a** was thermodynamically the most stable isomer and that the unwanted C-2 epimer could be isomerized to provide **11** under acidic conditions. We have also employed isoxazoline chemistry in the nikkomycin area.[7] Thus sequential reaction of 4-methoxybenzaldehyde with trianion **12** and

(1) (a) Zähner, H.; Holst, H.; Zoebelein, G.; Keckeisen, A. U.S. Patent 4 287 186, 1981. (b) König, W. A.; Hass, W.; Dehler, W.; Fiedler, H.-P.; Zähner, H. *Liebigs Ann. Chem.* **1980**, 622. (c) Dähn, U.; Hagenmaier, H.; Höhne, H.; König, W. A.; Wolf, G.; Zähner, H. *Arch. Microbiol.* **1976**, *107*, 143. (d) Hagenmaier, H.; Keckeisen, A.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1979**, 1494. (e) König, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Bormann, C.; Dehler, W.; Kurth, R.; Zähner, H. *Liebigs Ann. Chem.* **1986**, 407. (f) Hagenmaier, H.; Keckeisen, A.; Dehler, W.; Fiedler, H.-P.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1981**, 1018. (g) Delzer, J.; Fiedler, H.-P.; Müller, H.; Zähner, H.; Rathmann, R.; Ernst, K.; König, W. A. *J. Antibiot.* **1984**, *37*, 80.

(2) (a) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron Lett.* **1980**, *21*, 3395. (b) Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709. (c) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron* **1982**, *38*, 1599.

(3) Fiedler, H.-P.; Kurth, R.; Langhärig, J.; Delzer, J.; Zähner, H. *J. Chem. Tech. Biotechnol.* **1982**, *32*, 271.

(4) (a) Zimmerman, G.; Hass, W.; Faasch, H.; Schmalle, H.; König, W. A. *Liebigs Ann. Chem.* **1985**, 2165. (b) Hass, W.; König, W. A. *Liebigs Ann. Chem.* **1982**, 1615.

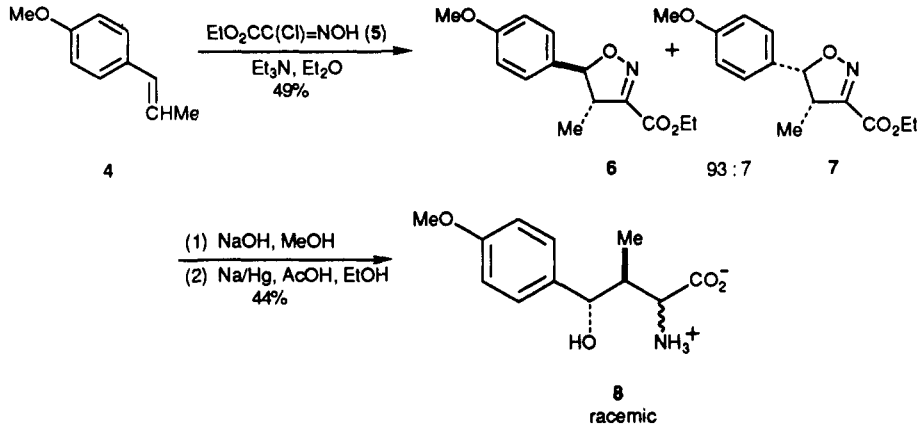
(5) Hahn, H.; Heitsch, H.; Rathmann, R.; Zimmerman, G.; Bormann, C.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1987**, 803.

(6) Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Müller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039.

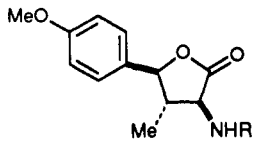
(7) (a) Banks, B. J.; Barrett, A. G. M.; Russell, M. A.; Williams, D. J. *J. Chem. Soc. Chem. Commun.* **1983**, 873. (b) Barrett, A. G. M.; Dhanak, D.; Lebold, S. A.; Russell, M. A. *J. Org. Chem.* **1991**, *56*, 1894.

0022-3263/91/1956-4875$02.50/0

Scheme I

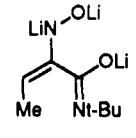


trifluoroacetic acid gave only the trans-substituted isoxazoline **13**. In addition, reduction of **13**, in contrast to **6**, stereoselectively gave mostly the required amino acid **14a**, and this was converted into the γ-lactone **11b**. In spite of these successes, we were unsuccessful in converting **11b** into the protected γ-hydroxy-α-amino acid **14d**. For example, although lactone **11b** was successfully converted into amide **14b**, ozonolysis resulted in partial C-2 epimerization and gave indole **14c** as a mixture of isomers.[8] We have widely and successfully used this indole methodology in the carbohydrate area,[9] and its failure for substrate **14c** is surprising. Suitably chastized by these experiences we vowed to prepare nikkomycin B (**1**) without proceeding through isoxazolines and γ-lactones such as **11**. Weinreb and co-workers have also reported a non-isoxazoline strategy to prepare the nikkomycin B N-terminal amino acid residue.[10] This group employed a Diels–Alder cyclization process to elaborate **15** and subsequently the γ-lactone **11c**. Herein we report details on an enantioselective and diastereoselective acyclic method to prepare a derivative of the nikkomycin B N-terminal amino acid **16**[1b,4a,11] and its coupling with uracil polyoxin C (**17**)[12] to provide nikkomycin B (**1**).[13]



11

(a) R = H_2 Cl
(b) R = $CO_2CH_2CH_2SiMe_3$
(c) R = COPh



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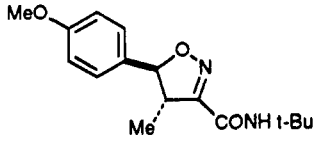

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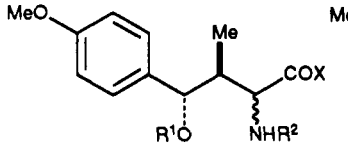
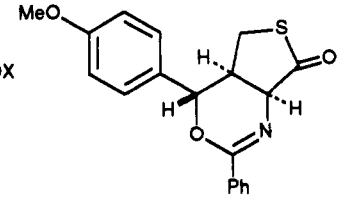


14

(a) X = NH t-Bu, $R^1 = R^2 = H$
(b) X = NHC_6H_4-2-$CH_2CH{=}CH_2$, R^1 = H, $R^2 = CO_2CH_2CH_2SiMe_3$
(c) X = 1-indolyl, $R^1 = CH_2OCH_2CH_2SiMe_3$, $R^2 = CO_2CH_2CH_2SiMe_3$
(d) X = OH, $R^1 = CH_2OCH_2CH_2SiMe_3$, $R^2 = CO_2CH_2CH_2SiMe_3$



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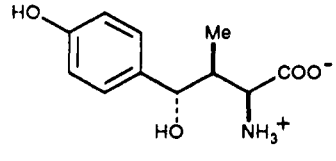

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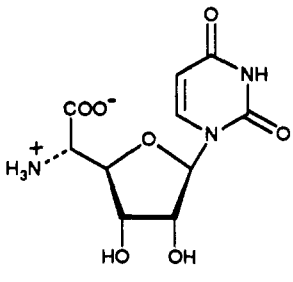

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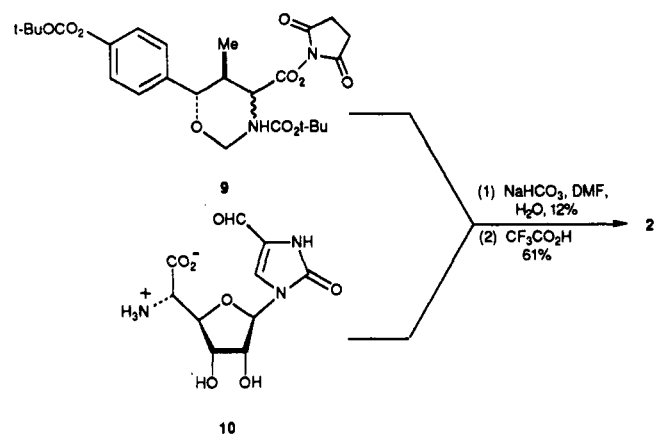
Scheme II

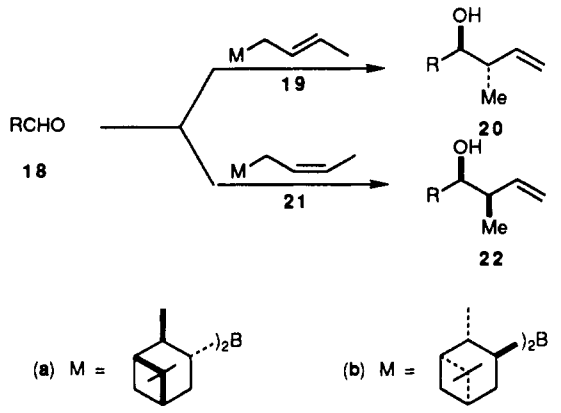


Synthesis of the N-Terminal Amino Acid Unit

The addition of crotylmetal species to aldehydes is a powerful method for the diastereoselective synthesis of

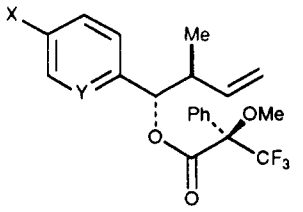
(8) Barrett, A. G. M.; Dhanak, D., unpublished observations.
(9) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Dhanak, D.; Gasiecki, A. F.; Howell, A. R.; Lee, A. C.; Russell, M. A. *J. Org. Chem.* **1989**, *54*, 3321.
(10) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850.
(11) König, W. A.; Pfaff, K.-P.; Bartsch, H.-H.; Schmalle, H.; Hagenmaier, H. *Liebigs Ann. Chem.* **1980**, 1728.
(12) (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (b) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812. (c) Jones, G. H.; Moffatt, J. G.; Edge, M. D. U.S. Patent 3 935 184, 1976. (d) Rathmann, R.; König, W. A.; Schmalle, H.; Carlsson, G.; Bosch, R.; Hagenmaier, H.; Winter, W. *Liebigs Ann. Chem.* **1984**, 1216. (e) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853. (f) Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019.
(13) Preliminary communication: Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 5818.

Scheme III



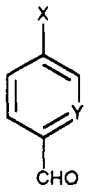
either anti or syn homoallylic alcohols **20** or **22**[14] (Scheme III). Since these reactions proceed via six-center chairlike transition states the *E* reagents **19** are anti selective and the *Z* reagents **21** syn. The crotyldiisopinocampheylboranes **19a**, **19b**, **21a**, and **21b**, introduced by Brown,[15] are particularly useful reagents since they react with aldehydes **18** to produce either the anti or syn adducts **20** or **22** with both excellent relative stereochemical control and high enantioselectivity. Additionally, these reagents are easy to prepare optically pure on a large scale from inexpensive commercially available reagents. This methodology proved to be particularly useful in the nikkomycin area.

Reaction of 4-(pivaloyloxy)benzaldehyde (**23**)[16] with (−)-(*E*)-crotyldiisopinocampheylborane (**19a**), the reagent derived from (+)-(α)-pinene, gave the corresponding homoallylic alcohol **24** on alkaline hydrogen peroxide workup. Chromatography gave the required 3*S*,4*S* compound **24** as a single diastereoisomer. Examination of the 400-MHz ^{1}H NMR spectrum of the crude alcohol **24** showed the diastereoselectivity of reaction to be at least 96:4. The alcohol **24** was converted into the corresponding (*R*)-Mosher ester **28a**, and this was also shown to be at least 98:2 diastereoisomerically pure by ^{1}H NMR spectroscopy. Clearly, this ratio reflected the enantiomeric excess in the crotonylation reaction. In contrast to aldehyde **23**, neither **29a** nor **29b** were satisfactory substrates for Brown homologation. Partial debenzoylation was a complication with **29a** and the homoallylic alcohol from **29b** and **19a** was formed with reduced diastereoselectivity (≤8:1). Presumably, **29b** was less electrophilic than **23** and slower to react thus allowing for *E*/*Z* isomerization of the Brown reagent. 2-Pyridinecarboxaldehyde (**29c**) was allowed to react with **19a** to provide the homoallylic alcohol **30a** in modest yield (31%). Again, examination of the ^{1}H NMR spectrum of the crude product **30a** and (*R*)-Mosher ester **28a** showed that the diastereoselectivity of reaction was excellent >96:4 and enantioselectivity reasonable (83% ee). *tert*-Butyldiphenylsilylation[17] of **24** and **30a** respectively gave **25** (97%) and **30b** (98%), and these products were ozonolyzed with a dimethyl sulfide workup to provide the protected β-hydroxy aldehydes **26** (84%) and **30c** (93%). In the pyridine system ozonolysis was carried out under acidic conditions to prevent any N-oxidation.



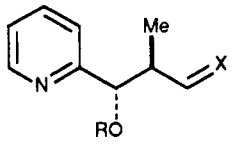
28

(a) X = t-BuCO$_2$, Y = CH
(b) X = H, Y = N



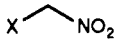
29

(a) X = PhCO$_2$, Y = CH
(b) X = t-BuPh$_2$SiO, Y = CH
(c) X = H, Y = N



30

(a) R = H, X = CH_2
(b) R = t-BuPh$_2$Si, X = CH_2
(c) R = t-BuPh$_2$Si, X = O



31

(a) X = SPh
(b) X = OCH_2Ph

Originally we planned to convert **25** into the corresponding α-amino acid using nitroalkene chemistry.[12e] Unfortunately, attempted Henry reaction of aldehyde **26** with (phenylthio)nitromethane (**31a**) or (benzyloxy)-nitromethane (**31b**) were unsuccessful due to facile β-elimination of the *tert*-butyldiphenylsilyloxy substituent and as a result nitroalkene **27** could not be isolated. However, (1-ethoxyvinyl)lithium[18] smoothly added to the aldehyde **26** to provide the α-hydroxy ester **32** on workup with ozone (Scheme V). Chromatography gave the major α-hydroxy ester **32** (43–51%) and the *R*,*S*,*S* diastereoisomer **33** (6%). Presumably the stereoselectivity of reaction was the result of Felkin Ahn control.[19] Structural assignments of the two diastereoisomers **32** and **33** were easily carried out after conversion into the two lactones **34** and **35**. Thus desilylation and cyclization of **32** and **33** respectively gave **34** and **35** in unoptimized yields of 27 and 25%. The two isomers were easily distinguished by the magnitude of the 3-H, 4-H coupling constants[6] in the ^{1}H NMR spectra [**34**, $J_{3,4}$ = 10.4 Hz; **35**, $J_{3,4}$ = 8.0 Hz]. There was no overlap in either crude reaction mixture. No lactone **35** was detected in the reaction mixture from alcohol **32** and no lactone **34** was formed from **33**.

Introduction of the α-amino functionality was achieved by conversion of the hydroxy ester **32** to the iodide **36** (85%)[20] followed by nucleophilic displacement with sodium azide in DMF,[21] affording the desired (2*S*)-α-azido ethyl ester **37** (91%) (Scheme VI). Although saponification of the ester **37** led to undesired desilylation and lactonization, ester **37** could be hydrolyzed under nonaqueous conditions developed in our laboratories.[22] Transesterification of **37** in the presence of 3-buten-1-ol and Ti(O*i*-Pr)$_4$[23] gave the

(14) For examples, see: (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (e) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (f) Garcia, J.; Kim, B.-M.; Masamune, S. J. *J. Org. Chem.* **1987**, *52*, 4831. (g) Rousch, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (h) Rousch, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (i) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129.

(15) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293; **1986**, *108*, 5919.

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(19) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

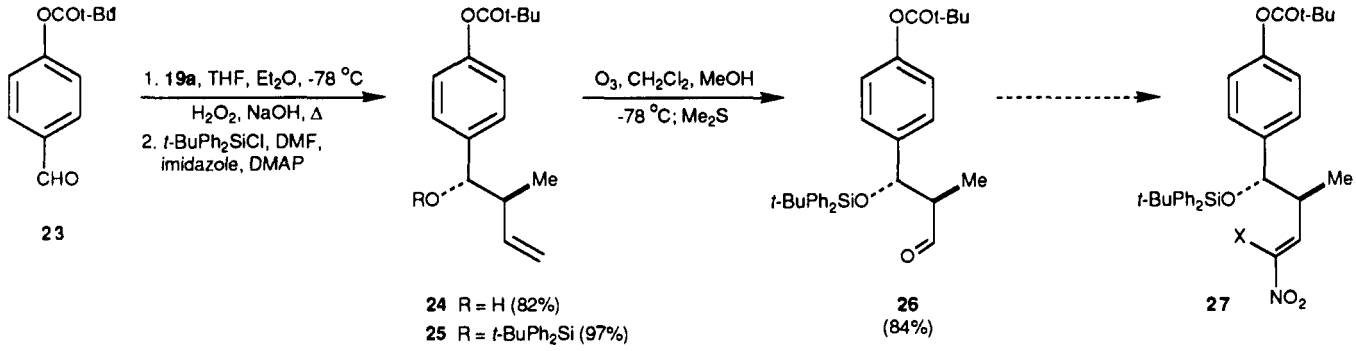
(20) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1970**, *35*, 2319.

(21) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1 and references therein.

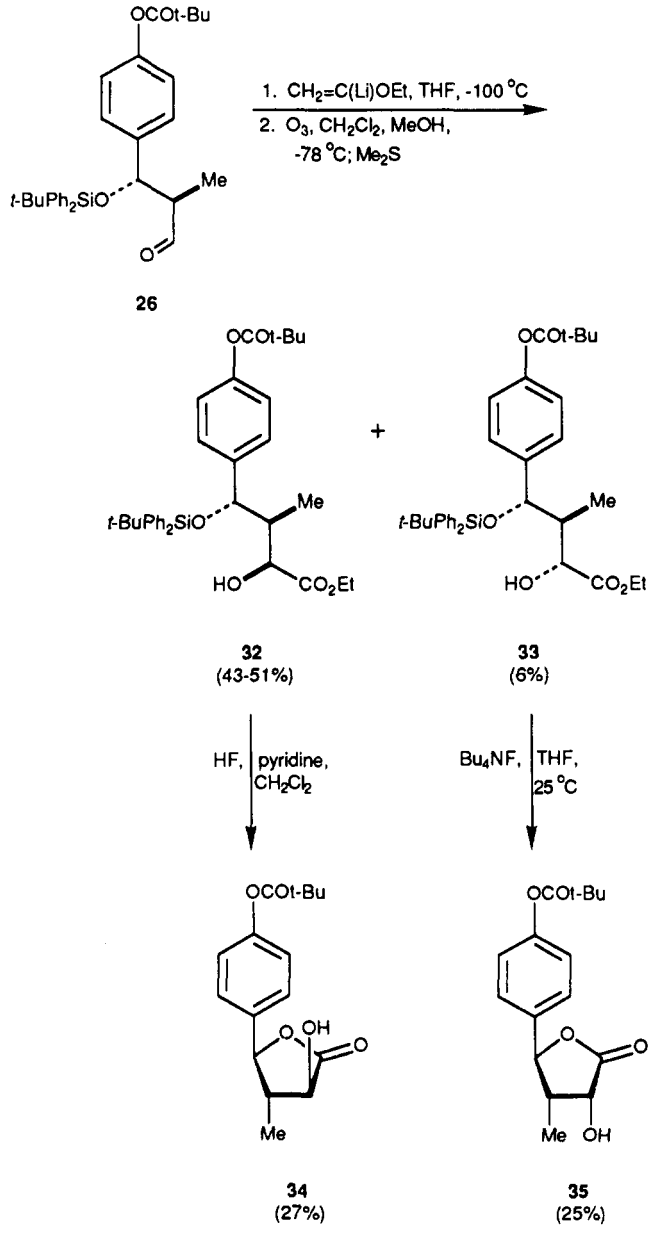
(22) Barrett, A. G. M.; Lebold, S. A.; Zhang, X.-A. *Tetrahedron Lett.* **1989**, *30*, 7317.

(23) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

Scheme IV



Scheme V



ester **38** (91%), which was protected as the *tert*-butyldimethylsilyl ether **39** (95%).[24] Ozonolysis of the butene residue afforded the aldehyde **40**, which, after treatment with DBU[22] in situ, gave the α-azido acid. Without isolation, treatment of the crude acid with diazomethane gave the corresponding methyl ester in a good overall yield (73%). Alternatively, esterification using *p*-nitrophenol and DCC in THF[25] afforded the activated ester **16** (61%).

Synthesis of Nikkomycin B (1)

Recently we described the synthesis of uracil polyoxin C (**17**) using as a key step the highly stereoselective addition of potassium trimethylsilanoate to the nitroalkene **42** to provide the α-hydroxy thioester **43** (Scheme VII). This substance was subsequently converted into **17** via the introduction of azide and Vorbrüggen glycosidation.[12e] The sample of uracil polyoxin C (**17**) prepared in this manner was identical with authentic material, which was kindly provided by Glaxo Group Research. The authentic **17** was protected as the benzyl ester,[25] Boc derivative.[26] Selective deprotection of the carbamate using trifluoroacetic acid[27] gave the corresponding amine trifluoroacetate salt, and this was used directly in the peptide coupling reaction. Thus reaction of this salt with the 4-nitrophenyl ester **41**[27,28] in the presence of 4-methylmorpholine in DMF[29] gave the corresponding nucleoside dipeptide **45** (53%). Attempted direct coupling of uracil polyoxin C (**17**) and the 4-nitrophenyl ester **41** was unsuccessful due to low solubility of either component in various solvent mixtures. Desilylation[17] of **45** followed by selective hydrogenolysis of the benzyl ester[12c] and azide gave nikkomycin B (**1**). The product was isolated in modest yield by chromatography on cellulose. Attempted deprotection of dipeptide **45** by hydrogenolysis followed by desilylation was unsuccessful. In addition, attempted selective hydrogenolysis using palladium on carbon was also unsatisfactory. Using these methods, dehydroxylation of the γ-hydroxy group was a major complication.

We have been unable to secure a sample of authentic nikkomycin B (**1**). However, our synthetic material shows properties that are in good agreement, with the exception of the nucleoside base, with data published by König for nikkomycin B_x (**2**).[5] Important representative data is provided in Table I. For comparison, the data for the nikkomycin B_x diastereoisomer **46** is also provided. The N-terminal amino acid residue of synthetic **1** must have the natural 2*S*,3*S*,4*S* stereochemistry. This assignment is secure for four reasons. Firstly, the 3*S*,4*S* absolute stereochemistry follows from the extensive Brown pre-

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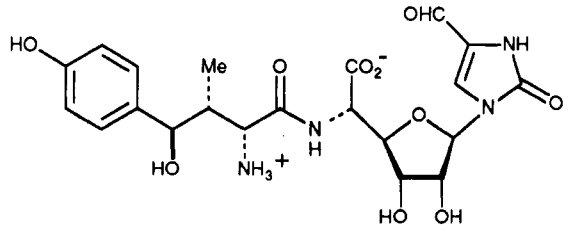

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cedent using borane **19a**.[8] Secondly, the preparation of γ-lactones **34** and **35** confirmed that the relative stereochemistry was either 2*S*,3*S*,4*S* or 2*R*,3*R*,4*R*. Thirdly, the comparisons of [α] and ^{1}H NMR spectra of synthetic **1**, **2**, and **46** (Table I) are fully consistent with the 2*S*,3*S*,4*S* assignment. Fourthly, the synthetic **1** cannot possibly have the 2*R*,3*S*,4*S* stereochemistry since the C*H*-NH_2 proton has too small a *J* value[4a] (δ 4.05 (br s, 1 H)). Thus C-2 epimerization did not take place either during the synthesis of the α-azido ester **41** or during peptide construction.[30]

In conclusion, a potentially general route to the (2*S*,3*S*,4*S*)-γ-hydroxy-β-methyl-α-aminobutanoic acid moiety, a common feature of the nikkomycin N-terminal amino acid residues, has been described. The protected α-amino nucleoside fragment **44** has been successfully coupled with the activated *p*-nitrophenyl ester **41** completing the total synthesis of nikkomycin B (**1**). The strategy should be general for other nikkomycins, for example aldehyde **30c** should be useful for the preparation of nikkomycin J (**3**) and analogues.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry N_2 at room temperature in oven-dried glassware unless otherwise noted. Reaction temperatures were recorded as bath temperatures. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN, or G. D. Searle and Co., Skokie, IL. Column chromatography was performed on E. Merck silica gel 60, 230–400 mesh ASTM. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates.

Solvents for chromatography were distilled at atmospheric pressure prior to use. Hexanes refer to the ACS reagent boiling range 35–60 °C. Anhydrous THF and CH_2Cl_2 were respectively distilled from Na/benzophenone ketal and CaH_2. DMF was dried by distillation at reduced pressure from BaO and stored over 4-Å molecular sieves. MeOH was dried by distillation from Mg and stored over 3-Å sieves. All other chemicals were used without further purification unless otherwise noted. All solvents used to extract aqueous solutions were dried with either $MgSO_4$ or Na_2SO_4 and evaporated in vacuo on a rotary evaporator at or below 40 °C. Reported yields refer to chromatographically and spectroscopically homogeneous material.

(3*S*,4*S*)-4-Hydroxy-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]butene (24). To *t*-BuOK (1 M in THF; 30 mL) and *trans*-2-butene (60 mmol, 6 mL) at −78 °C was added *n*-BuLi (1.8 M in hexanes; 16.7 mL). The solution was allowed to warm to −45 °C for 10 min and then recooled to −78 °C, and (−)-*B*-methoxydiisopinocampheylborane (1 M in Et_2O; 72 mmol, 36 mL) was added dropwise. The reaction mixture was maintained at −78 °C for 30 min and BF_3·Et_2O (40.2 mmol, 5 mL) was added followed by the dropwise addition of the aldehyde **23** (17 mmol, 3.5 g) in anhydrous Et_2O (10 mL). The reaction mixture was kept at −78 °C for 4.5 h, allowed to warm up to 0 °C, and quenched by the careful addition of aqueous NaOH (3 M; 50 mL) followed by 30% H_2O_2 (9 mL). The mixture was heated to reflux for 12 h and cooled, and the organic layer was separated. This was washed in NaOH (1 M; 25 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (4:1 CH_2Cl_2/Et_2O) to afford the homoallylic alcohol **24** (3.66 g, 82%) as a colorless oil, which contained only a single diastereoisomer as judged by ^{1}H NMR spectroscopy, thus the diastereoselectivity of the reaction was at least 96:4: $[\alpha]_D$ −64.4° (*c* 1.03 in $CHCl_3$); IR (neat) 3460 (br), 3103, 3002, 2961, 2938, 2902, 1764, 1652, 1623, 1516, 1491, 1469, 1441, 1409, 1383, 1287, 1243, 1210, 1175, 1131, 1037, 1025, 924, 906 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32, 7.03 (AB q, 4 H, *J* = 8.6 Hz), 5.79 (m, 1 H), 5.18 (d, 1 H, *J* = 7.8 Hz), 5.16 (s, 1 H), 4.35 (d, 1 H, *J* = 7.8 Hz), 2.44 (m, 1 H), 2.25 (br s, 1 H), 1.35 (s, 9 H), 0.86 (d, 1 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 150.4, 140.4, 139.7, 127.7, 121.1, 116.8, 77.2, 46.2, 39.0, 27.1, 16.4; MS (FAB) *m*/*z* 263 (M + H$^+$), 261, 245, 207, 191, 161, 136, 123, 107; exact mass (FAB) calcd for $C_{16}H_{22}O_3$ (M + H$^+$) 263.1648, found (M + H$^+$) 263.1638. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.09; H, 8.48.

(3*S*,4*S*)-4-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetoxy]-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]-phenyl]butene (28a). To the alcohol **24** (50 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (1 mL) was added (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.38 mmol, 89 mg), followed by DCC (0.38 mmol, 79 mg) and a catalytic amount of DMAP. The reaction mixture was stirred at 25 °C and after 2 h, diluted with Et_2O (10 mL), filtered through a glass wool plug, and washed successively with aqueous $NaHSO_4$ (0.5 M; 5 mL), brine (5 mL), and saturated aqueous $NaHCO_3$ (5 mL), followed again by brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated to yield the crude ester **28a** as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) showed that the oil contained only a single diastereoisomer, thus the enantiomeric excess of the reaction was greater than the limits of detection of the instrument (>96% ee). The residue was chromatographed on silica gel (1:9 Et_2O/hexanes) to give the pure Mosher ester **28a** (85 mg, 93%) as a colorless oil: IR (neat) 3090, 2998, 2898, 1753, 1611, 1509, 1483, 1457, 1429, 1402, 1373, 1274, 1161, 1121, 1011, 999, 927, 900, 842, 811, 770, 723, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 7.19, 6.99, (AB q, 4 H, *J* = 8.6 Hz), 5.78 (m, 1 H), 5.71 (d, 1 H, *J* = 8.2 Hz), 5.11 (d, 1 H, *J* = 7 Hz), 5.08 (s, 1 H), 3.51 (s, 3 H), 2.70 (m, 1 H), 1.36 (s, 9 H), 0.88 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 165.7, 151.0, 139.2, 134.8, 132.1, 129.4, 128.4, 128.2, 127.3, 123.3, (q, J_{CF} = 290 Hz), 121.3, 116.5, 84.6 (q, J_{CF} = 28 Hz), 81.6, 55.8, 42.9, 39.1, 27.1, 16.5; MS (EI) *m*/*z* 478 (M$^{\cdot+}$), 435, 423, 245, 189, 161, 105, 83, 57; exact mass (EI) calcd for $C_{26}H_{29}F_3O_5$ (M$^{\cdot+}$) 478.1967, found (M$^{\cdot+}$) 478.1937.

(3*S*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]butene (25). To the alcohol **24** (3.7 g, 14 mmol) in DMF (10 mL) were added imidazole (28 mmol, 2.0 g), *tert*-butylchlorodiphenylsilane (14 mmol, 3.7 mL), and a catalytic amount of DMAP. The reaction mixture was stirred at 60 °C for 12 h, poured into H_2O (50 mL), and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with pH 4 phthalate buffer, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (5:95 Et_2O/hexanes) to afford the silyl ether **25** (6.88 g, 97%) as a colorless oil: $[\alpha]_D$ −56.2° (*c* 0.95 in $CHCl_3$); IR (neat) 3100, 2975, 2987, 2956, 2884, 1767, 1617, 1604, 1506, 1487, 1475, 1448, 1405, 1377, 1289, 1213, 1177, 1125, 1079, 1038, 1027, 1009, 927, 907, 865, 836, 753, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.20 (m, 10 H), 7.16, 6.91 (AB q, 4 H, *J* = 8.4 Hz), 5.52 (m, 1 H), 4.86 (dd, 1 H, *J* = 10.3, 1.8 Hz), 4.76 (d, 1 H, *J* = 17.2 Hz), 4.58 (d, 1 H, *J* = 5.4 Hz), 2.41 (m, 1 H), 1.36 (s, 9 H), 1.04 (s, 9 H), 0.79 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 150.1, 140.9, 139.4, 136.0, 135.9, 134.2, 133.6, 129.6, 129.4, 128.1, 127.4, 127.3, 120.4, 114.8, 79.0, 45.8, 39.1, 27.2, 27.1, 19.4, 14.4; MS (FAB) *m*/*z* 501, 500 (M$^{\cdot+}$), 499, 445, 423, 361, 245, 237, 197, 161, 135; exact mass (FAB) calcd for $C_{32}H_{40}O_3Si$ (M$^{\cdot+}$) 500.2748, found (M$^{\cdot+}$) 500.2756. Anal. Calcd for $C_{32}H_{40}O_3Si$: C, 76.76; H, 8.05. Found: C, 76.52; H, 8.06.

(2*S*,3*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methyl-3-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]propanal (26). To the alkene **25** (3.4 g, 6.8 mmol) in 1:1 CH_2Cl_2/MeOH (100 mL) at −78 °C was introduced ozone via a pipette until a blue color persisted. The solution was purged of excess ozone with a stream of N_2, Me_2S (25 mL) was added, and the reaction mixture warmed up to 25 °C. After 12 h the reaction mixture was poured into H_2O (100 mL) and the organic layer separated. The aqueous layer was

(30) For a recent example of the use of α-azido acids for the "racemization free" synthesis of peptides, see: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

Scheme VI

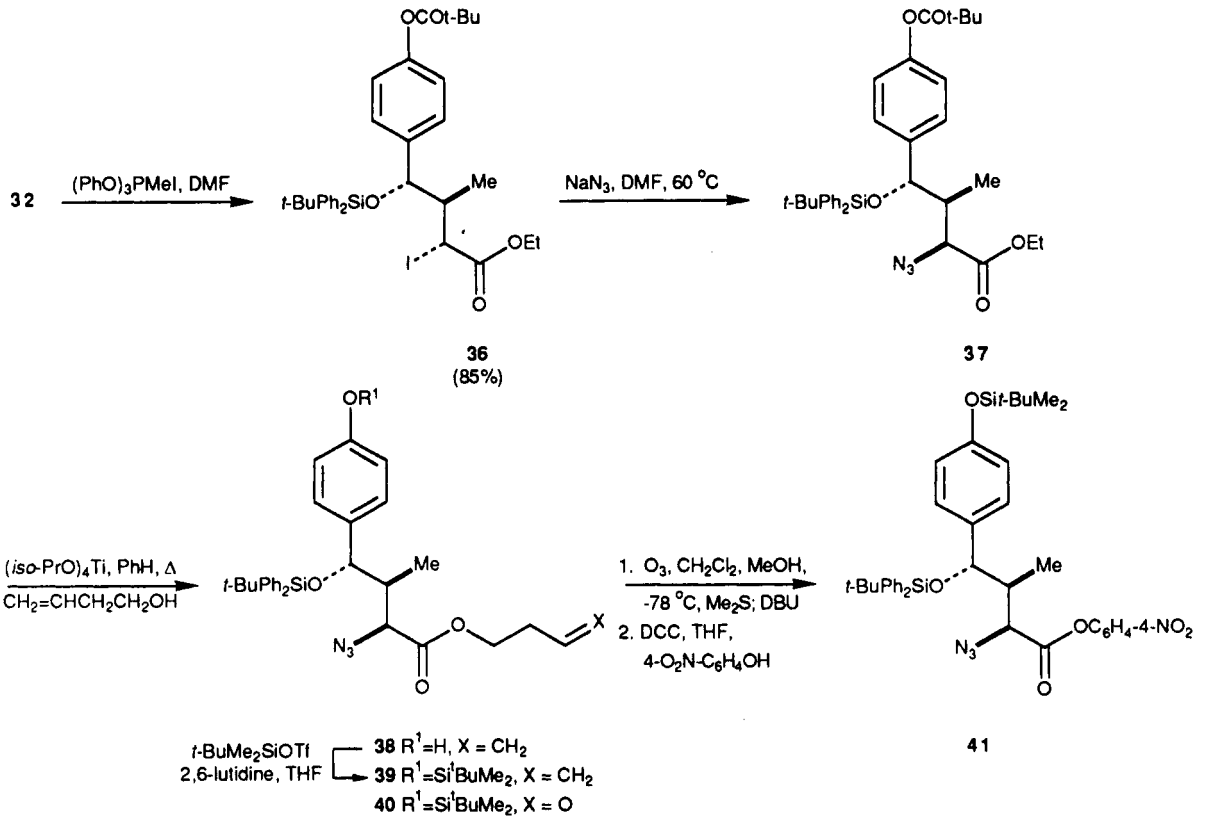


Table I. Comparison of ^{1}H NMR Data (400 MHz, D_2O/CD_3OD) for Synthetic Nikkomycin B (1), Synthetic Nikkomycin B_x (2),[5] and (2*R*,3*R*,4*R*)-Nikkomycin B_x (46)[5]

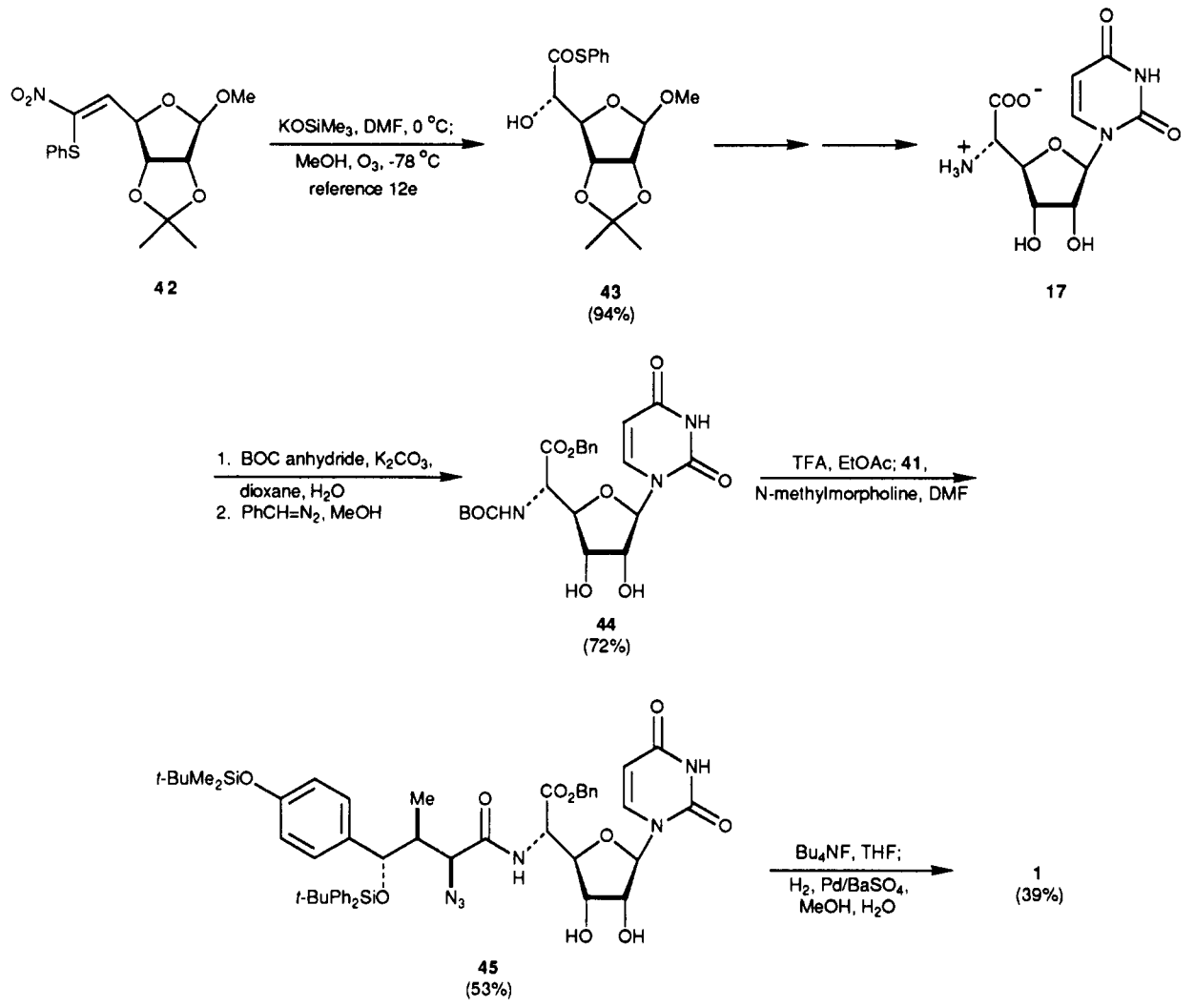
	1	2	46
$[\alpha]_D$	+50° (*c* 0.04 in H_2O)	+56.7° (*c* 0.06 in H_2O)	+27.5° (*c* 0.04 in H_2O)
	7.65 (d, 1 H, *J* = 8.2 Hz, base 6-H)	9.08 (s, 1 H, CHO)	9.06 (s, 1 H, CHO)
	5.85 (d, 1 H, *J* = 8.2 Hz, base 5-H)	7.54 (s, 1 H, base 5-H)	7.39 (s, 1 H, base 5-H)
	7.27, 6.88 (AB q, 4 H, *J* = 8 Hz, aryl-H)	7.11, 6.71 (AB q, 4 H, *J* = 8.8 Hz, aryl-H)	7.05, 6.67 (AB q, 4 H, *J* = 8.8 Hz, aryl-H)
	5.81 (d, 1 H, *J* = 5.4 Hz, 1′-H)	5.40 (d, 1 H, *J* = 5.8 Hz, 1′-H)	5.40 (d, 1 H, *J* = 6.0 Hz, 1′-H)
	4.51 (d, 1 H, *J* = 5.6 Hz, 5′-H)	4.35 (d, 1 H, *J* = 4.3 Hz, 5′-H)	4.35 (d, 1 H, *J* = 3.6 Hz, 5′-H)
	4.40 (app. t, 1 H, *J* ≈ 5 Hz, 3′-H)	4.31 (dd, 1 H, *J* = 4.4, 5.5 Hz, 3′-H)	4.33 (dd, 1 H, *J* = 4.4, 5.8 Hz, 3′-H)
	4.25 (app. t, 1 H, *J* = 5.4 Hz, 2′-H)	4.22 (dd, 1 H, *J* = 5.8, 5.5 Hz, 2′-H)	4.26 (dd, 1 H, *J* = 6.0, 5.8 Hz, 2′-H)
	4.21 (app. t, 1 H, *J* = 4.6 Hz, 4′-H)	4.08 (dd, 1 H, *J* = 4.4, 4.3 Hz, 4′-H)	4.13 (dd, 1 H, *J* = 4.4, 3.6 Hz, 4′-H)
	4.51 (d, 1 H, *J* = 9 Hz, 4″-H)	4.39 (d, 1 H, *J* = 8.2 Hz, Hz, 4″-H)	4.38 (d, 1 H, *J* = 9.6 Hz, 4″-H)
	4.05 (br s, 1 H, 2″-H)	4.07 (d, 1 H, *J* = 2.8 Hz, 2″-H)	4.13 (d, 1 H, *J* = 4.8 Hz, 2″-H)
	2.43 (m, 1 H, 3″-H)	2.36 (m, 1 H, 3″-H)	2.20 (m, 1 H, 3″-H)
	0.67 (d, 3 H, *J* = 6.9 Hz, 3″-CH_3)	0.63 (d, 3 H, *J* = 7.2 Hz, 3″-CH_3)	0.58 (d, 3 H, *J* = 7.2 Hz, 3″-CH_3)

extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with H_2O (100 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (1:9 ethyl acetate/hexanes) to give the aldehyde **26** (2.87 g, 84%) as a colorless oil: $[\alpha]_D$ −91.3° (*c* 1.56 in $CHCl_3$); IR (neat) 3087, 3066, 2977, 2952, 2877, 2730, 1754, 1729, 1606, 1594, 1501, 1474, 1438, 1393, 1364, 1276, 1201, 1166, 1110, 924, 895, 841, 820, 738, 699, 604 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, 1 H, *J* = 2.7 Hz), 7.62–7.23 (m, 10 H), 7.14, 6.93 (AB q, 4 H, *J* = 8.6 Hz), 4.88 (d, 1 H, *J* = 7.5 Hz), 2.72 (m, 1 H), 1.35 (s, 9 H), 1.01 (s, 9 H), 0.76 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 176.8, 150.5, 138.5, 135.9, 133.2, 132.8, 129.8, 129.6, 127.8, 127.6, 127.4, 121.2, 76.1, 54.5, 39.0, 27.1, 26.9, 19.3, 10.2; MS (FAB) *m*/*z* 501 (M − H$^+$), 445, 425, 361, 239, 197, 135; exact mass (FAB) calcd for $C_{31}H_{38}O_4Si$ (M − H$^+$) 501.2462, found (M − H$^+$) 501.2477. Anal. Calcd for $C_{31}H_{38}O_4Si$: C, 74.07; H, 7.62. Found: C, 74.10; H, 7.81.

(3*S*,4*S*)-4-Hydroxy-3-methyl-4-(2-pyridyl)butene (30a). To *t*-BuOK (1 M in THF; 100 mL) and *trans*-2-butene (200 mmol, 20 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes; 10 mmol, 62.5 mL). The solution was allowed to warm up to −45 °C for 10 min and recooled to −78 °C, and (−)-*B*-methoxydiisopinocampheylborane (**19a**) (1.6 M in Et_2O; 92 mmol, 75 mL) was added dropwise. The mixture was stirred at −78 °C for a further 30 min, and BF_3·Et_2O (134 mmol, 16.5 mL) was added followed by the aldehyde **29c** (140 mmol, 13.5 mL) in anhydrous Et_2O (20 mL). The solution was stirred at −78 °C for 3 h and warmed up to 0 °C, and the reaction mixture was quenched by the addition of aqueous NaOH (3 M, 220 mmol, 74 mL) followed by 30% H_2O_2 (30 mL). The reaction mixture was heated to reflux for 1 h and cooled, and the organic layer was separated. This was washed with H_2O (120 mL) and brine (120 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (1:3 Et_2O/hexanes) to give the homoallylic alcohol **30a** (5.0 g, 31%) as a colorless oil, which contained only a single diastereoisomer as judged by ^{1}H NMR spectroscopy, thus the diastereoselectivity of the reaction was at least 96:4: $[\alpha]_D$ −62.1° (*c* 1.16 in $CHCl_3$); IR (neat) 3400 (br), 3092, 2995, 1646, 1601, 1579, 1480, 1441, 1420, 1320, 1158, 1132, 1058, 1041, 1009, 920, 756, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, 1 H, *J* = 4.8 Hz), 7.66 (dt, 1 H, *J* = 7.6, 1.6 Hz), 7.26 (d, 1 H, *J* = 8 Hz), 7.18 (m, 1 H), 5.76 (m, 1 H), 4.98 (m, 2 H), 4.64 (d, 1 H, *J* = 4.4 Hz), 4.33 (br s, 1 H), 2.67 (m, 1 H), 1.06 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 149.1, 139.2, 136.3, 122.3, 121.2, 115.9, 76.3, 44.9, 16.1; MS (EI) *m*/*z* 164 (M + H$^+$), 163 (M$^{\cdot+}$), 148, 108; exact mass (EI) calcd for $C_{10}H_{13}NO$ (M$^{\cdot+}$) 163.0997, found (M$^{\cdot+}$) 163.1001.

(3*S*,4*S*)-4-[(*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetoxy]-3-methyl-4-(2-pyridyl)butene (28b). To the alcohol **30a** (20 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (1 mL) were added

Scheme VII



(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.25 mmol, 57 mg) and DMAP (0.08 mmol, 5 mg), followed by DCC (0.49 mmol, 51 mg). The reaction mixture was stirred at 25 °C and after 2 h, diluted with Et_2O (10 mL) and filtered through a glass wool plug. The solution was washed with $NaHSO_4$ (1 M; 10 mL), brine (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and once again with brine (10 mL), dried ($MgSO_4$), and evaporated to yield the crude Mosher ester **28b** (42 mg, 91%) as a colorless oil. The ^1H NMR spectrum (400 MHz, $CDCl_3$) showed that the oil contained an 11:1 mixture of diastereoisomers, major isomer: δ 8.59 (m, 1 H), 7.64–7.03 (m, 8 H), 5.92 (d, 1 H, *J* = 6.4 Hz), 5.77 (m, 1 H), 5.03 (d, 1 H, *J* = 11.6 Hz), 4.99 (d, 1 H, *J* = 17.2 Hz), 3.56 (s, 3 H), 2.96 (m, 1 H), 1.02 (d, 3 H, *J* = 6.8 Hz).

(3*S*,4*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-4-(2-pyridyl)butene (30b). To the alcohol **30a** (140 mg, 0.86 mmol) in DMF (0.5 mL) was added imidazole (1.7 mmol, 0.12 g) and *tert*-butylchlorodiphenylsilane (0.86 mmol, 0.22 mL) followed by a catalytic amount of DMAP. The reaction mixture was stirred for 48 h and poured into H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (3:7 Et_2O/hexanes) to give the silyl ether **30b** (338 mg, 98%) as a colorless oil: $[\alpha]_D$ −30.2° (*c* 2.58 in $CHCl_3$); IR (neat) 3087, 2989, 2935, 2908, 2878, 1650, 1596, 1577, 1475, 1442, 1395, 1365, 1266, 1192, 1115, 1076, 1047, 1004, 908, 846, 825, 744, 704, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, *J* = 4.8 Hz), 7.73–7.02 (m, 13 H), 5.76 (m, 1 H), 4.88 (dd, 1 H, *J* = 10.3, 1.4 Hz), 4.85 (d, 1 H, *J* = 4.8 Hz), 4.75 (d, 1 H, *J* = 17.3 Hz), 2.55 (m, 1 H), 1.07 (s, 9 H), 0.83 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 148.0, 140.2, 136.1, 136.0, 135.5, 134.8, 129.6, 129.4, 127.7, 127.4, 127.3, 122.1, 121.8, 114.7, 80.6, 45.4, 27.2, 26.6, 19.6, 15.8; MS (EI) *m*/*z* 401 ($M^{\bullet+}$), 344, 289, 199, 135; exact mass (EI) calcd for $C_{28}H_{31}NOSi$ ($M^{\bullet+}$) 401.2175, found ($M^{\bullet+}$) 401.2155.

(2*S*,3*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-2-methyl-3-(2-pyridyl)propanal (30c). To the alkene **30b** (338 mg, 0.84 mmol) in anhydrous CH_2Cl_2 (3 mL) was added *p*-TsOH·H_2O (0.84 mmol, 0.16 g). The reaction mixture was cooled to −78 °C, and ozone was introduced via a pipette until a blue color persisted. The reaction mixture was purged of excess ozone with a stream of N_2, $(CH_3)_2S$ (2 mL) was added, and the mixture was warmed up to 25 °C. After 12 h, the solution was neutralized with saturated aqueous $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), evaporated, and recrystallized (Et_2O/hexanes) to yield the aldehyde **30c** (316 mg, 93%) as a white solid: mp 88–89 °C; $[\alpha]_D$ −100.3° (*c* 1.24 in $CHCl_3$); IR (KBr) 3210, 3188, 3150, 3130, 2995, 2890, 2810, 2774, 2750, 1735, 1609, 1489, 1449, 1423, 1411, 1367, 1333, 1309, 1281, 1261, 1130, 1097, 1061, 1029, 1015, 952, 930, 920, 862, 852, 840, 781, 771, 760, 721, 668, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, 1 H, *J* = 1.2 Hz), 8.39 (d, 1 H, *J* = 4.8 Hz), 7.70–7.06 (m, 13 H), 5.37 (d, 1 H, *J* = 4.8 Hz), 2.70 (m, 1 H), 1.11 (s, 9 H), 0.82 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 160.3, 148.4, 136.2, 135.8, 135.7, 133.1, 132.7, 130.0, 129.7, 127.7, 127.5, 122.2, 121.2, 76.3, 53.4, 27.0, 19.4, 8.5; MS (EI) *m*/*z* 403 ($M^{\bullet+}$), 375, 346, 302, 288, 268, 240, 199, 183, 135; exact mass (EI) calcd for $C_{25}H_{29}NO_2Si$ ($M^+ - C_4H_9^+$) 346.1263, found ($M^+ - C_4H_9^+$) 346.1265. Anal. Calcd for $C_{25}H_{29}NO_2Si$: C, 74.40; H, 7.24; N, 3.47. Found: C, 74.14; H, 7.40; N, 3.38.

(2*S*,3*S*,4*S*)-Ethyl 4-[(*tert*-Butyldiphenylsilyl)oxy]-2-hydroxy-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]-phenyl]butanoate (32). To ethyl vinyl ether (redistilled from Na; 1.0 mmol, 95 μL) in anhydrous THF (1 mL) at −78 °C was added *t*-BuLi (1.7 M in pentane; 0.5 mmol, 0.3 mL). After 15

min, the reaction mixture was allowed to warm up to 0 °C and maintained at that temperature for 30 min. The solution was recooled to −100 °C, and the aldehyde **26** (0.20 mmol, 100 mg) in anhydrous THF (1 mL) was added dropwise. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL), allowed to warm up to 25 °C, and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C, and ozone was introduced via a pipette until a blue color persisted. The solution was purged of excess ozone with a stream of N_2, Me_2S (1 mL) was added, and the reaction mixture was warmed up to 25 °C. After 18 h, the solution was poured into H_2O (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (1:9 ethyl acetate/hexanes, less polar diastereoisomer) to afford the α-hydroxy ester **32** (52 mg, 46%) as a colorless oil: $[\alpha]_D$ −38.2° (*c* 0.77, $CHCl_3$); IR (neat) 3523 (br), 3100, 3073, 2987, 2957, 2882, 1760, 1740, 1619, 1603, 1515, 1485, 1439, 1403, 1375, 1285, 1244, 1211, 1174, 1124, 1071, 1039, 905, 854, 832, 767, 750, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.20 (m, 10 H), 7.04, 6.81 (AB q, 4 H, *J* = 8.4 Hz), 4.81 (dd, 1 H, *J* = 5.2, 2 Hz), 4.59 (d, 1 H, *J* = 9.2 Hz), 4.25 (m, 2 H), 2.54 (d, 1 H, *J* = 5.2 Hz), 2.30 (m, 1 H), 1.34 (s, 9 H), 1.31 (t, 3 H, *J* = 7.2 Hz), 1.01 (s, 9 H), 0.42 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 175.3, 150.2, 139.9, 136.0, 133.6, 133.3, 129.5, 129.3, 128.2, 127.4, 127.2, 120.9, 76.9, 69.9, 61.6, 44.7, 39.0, 27.1, 27.0, 19.5, 14.3, 9.8; MS (EI) *m/z* 575 (M − H^+), 519, 501, 441, 417, 303, 267, 199, 135; exact mass (EI) calcd for $C_{34}H_{44}O_6Si$: (M − H^+) 575.2830, found (M − H^+) 575.2823. Anal. Calcd for $C_{34}H_{44}O_6Si$: C, 70.80; H, 7.69. Found: C, 70.94; H, 7.74. The more polar epimeric α-hydroxy ethyl ester **33** was obtained as a minor product (ca. 6%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.20 (m, 12 H), 6.89 (d, 2 H, *J* = 8.4 Hz), 4.63 (d, 1 H, *J* = 9.2 Hz), 4.15 (m, 2 H), 3.71 (dd, 1 H, *J* = 5.2, 2.4 Hz), 2.53 (d, 1 H, *J* = 4.8 Hz), 2.27 (m, 1 H), 1.36 (s, 9 H), 1.24 (t, 3 H, *J* = 7.2 Hz), 1.01 (s, 9 H), 0.88 (d, 3 H, *J* = 6.8 Hz).

(3*S*,4*S*,5*S*)-3-Hydroxy-4-methyl-5-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]tetrahydrofuran-2-one (34). To the ethyl ester **32** (0.138 g, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C was added a HF–pyridine complex (70% HF; 0.2 mL). After 2 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was purified by chromatography on silica gel (5:95 MeOH/$CHCl_3$) and recrystallization (CH_2Cl_2/Et_2O) to yield the trans lactone **34** (18.9 mg, 27%) as a white solid: mp 167–170 °C; $[\alpha]_D$ −28.9° (*c* 0.90 in $CHCl_3$); IR (KBr) 3455 (br), 2997, 2920, 1777, 1763, 1330, 1290, 1219, 1177, 1125, 1003, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37, 7.11 (AB q, 4 H, *J* = 8.8 Hz), 4.86 (d, 1 H, *J* = 10.4 Hz), 4.23 (d, 1 H, *J* = 10.8 Hz), 3.19 (br s, 1 H), 2.38 (m, 1 H), 1.36 (s, 9 H), 1.23 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 176.6, 151.7, 133.6, 127.7, 122.0, 83.5, 74.6, 47.5, 39.1, 27.1, 13.3; MS (EI) *m/z* 292 ($M^{\bullet+}$), 208, 164, 123, 107; exact mass (EI) calcd for $C_{16}H_{20}O_5$ ($M^{\bullet+}$) 292.1311, found ($M^{\bullet+}$) 292.1309. Anal. Calcd for $C_{16}H_{20}O_5 \cdot H_2O$: C, 61.92; H, 7.14. Found: C, 61.88; H, 6.70.

(3*R*,4*S*,5*S*)-3-Hydroxy-4-methyl-5-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]tetrahydrofuran-2-one (35). To the minor diastereoisomeric ethyl ester **33** (44 mg, 0.076 mmol) in anhydrous THF (1 mL) was added Bu_4NF (1.0 M in THF; 0.084 mmol, 84 μL). After 18 h, the mixture was poured into H_2O (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (3:7 ethyl acetate/hexanes) to afford the cis lactone **35** (5.5 mg, 25%) as a pale yellow oil: IR (neat) 3480 (br), 2988, 2952, 1790, 1758, 1513, 1482, 1462, 1370, 1266, 1210, 1172, 1116, 1002, 897, 852, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15, 7.10 (AB q, 4 H, *J* = 8.8 Hz), 5.64 (d, 1 H, *J* = 8 Hz), 4.18 (d, 1 H, *J* = 9.6 Hz), 2.81 (m, 1 H), 1.36 (s, 9 H), 0.88 (d, 3 H, *J* = 7.2 Hz); MS (EI) *m/z* 292 ($M^{\bullet+}$), 220, 199, 142, 123, 107; exact mass (EI) calcd for $C_{16}H_{20}O_5$ ($M^{\bullet+}$) 292.1311, found ($M^{\bullet+}$) 292.1310.

(2*R*,3*S*,4*S*)-Ethyl 2-Iodo-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]butanoate (36). To the alcohol **32** (1.0 g, 1.7 mmol) in DMF (5 mL) was added methyltriphenoxyphosphonium iodide (1.7 mmol, 0.8 g). After 18 h, the reaction mixture was diluted with EtOH (5 mL) and poured into saturated aqueous $Na_2S_2O_3$ (20 mL). The solution was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (15:85 Et_2O/hexanes), to give the iodide **36** (1.01 g, 85%) as a colorless oil: $[\alpha]_D$ −5.0° (*c* 0.80 in $CHCl_3$); IR (neat) 3082, 2982, 2942, 2870, 1762, 1742, 1461, 1435, 1376, 1284, 1262, 1211, 1172, 1120, 1083, 1028, 902, 856, 830, 745, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.7–7.2 (m, 12 H), 6.97 (d, 2 H, *J* = 8.5 Hz), 5.15 (d, 1 H, *J* = 4.1 Hz), 4.09 (q, 2 H, *J* = 7.1 Hz), 3.59 (d, 1 H, *J* = 10.9 Hz), 2.33 (m, 1 H), 1.37 (s, 9 H), 1.19 (t, 3 H, *J* = 7.1 Hz), 1.07 (s, 9 H), 0.94 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 170.3, 150.4, 137.0, 135.9, 135.8, 133.4, 133.1, 129.8, 129.6, 127.9, 127.7, 127.5, 120.8, 76.2, 61.6, 44.1, 39.0, 27.1, 27.0, 26.3, 19.3, 13.6, 11.0; MS (FAB) *m/z* 685 (M − H^+), 629, 609, 559, 502, 446, 445, 431, 361; exact mass (EI) calcd for $C_{34}H_{43}IO_5Si$: (M − $C_4H_9^+$) 629.1220, found (M − $C_4H_9^+$) 629.1215. Anal. Calcd for $C_{34}H_{43}IO_5Si$: C, 59.47; H, 6.31. Found: C, 59.50; H, 6.48.

(2*S*,3*S*,4*S*)-Ethyl 2-Azido-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methyl-4-[4-[(2,2-dimethylpropanoyl)oxy]phenyl]butanoate (37). To the iodide **36** (1.14 g, 1.7 mmol) in DMF (5 mL) was added NaN_3 (8.3 mmol), 0.54 g). The reaction mixture was stirred at 60 °C for 1 h, poured into H_2O (10 mL), and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (5:95 ethyl acetate/hexanes) to give the azide **37** (0.904 g, 91%) as a colorless oil: $[\alpha]_D$ −34.3° (*c* 0.91 in $CHCl_3$); IR (neat) 3091, 3070, 2990, 2952, 2878, 2119, 1748, 1609, 1592, 1507, 1480, 1462, 1430, 1392, 1369, 1277, 1201, 1167, 1113, 1073, 1030, 1019, 961, 900, 848, 823, 741, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.23 (m, 10 H), 7.07, 6.86 (AB q, 4 H, *J* = 8.4 Hz), 4.69 (d, 1 H, *J* = 2.8 Hz), 4.42 (d, 1 H, *J* = 9.3 Hz), 4.26 (m, 2 H), 2.47 (m, 1 H), 1.34 (s, 9 H), 1.31 (t, 3 H, *J* = 7.2 Hz), 0.99 (s, 9 H), 0.43 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 170.7, 150.5, 139.3, 135.9, 135.8, 133.5, 132.9, 129.7, 129.5, 128.3, 127.5, 127.3, 121.0, 76.6, 62.8, 61.8, 43.7, 39.0, 27.1, 27.0, 19.4, 14.2, 10.9; MS (FAB) *m/z* 600 (M − H^+), 544, 524, 445, 346, 318, 282, 227; exact mass (EI) calcd for $C_{34}H_{43}N_3O_5Si$ (M − $C_4H_9^+$) 544.2269, found (M − $C_4H_9^+$) 544.2295. Anal. Calcd for $C_{34}H_{43}N_3O_5Si$: C, 67.86; H, 7.20; N, 6.98. Found: C, 68.24; H, 7.29; N, 6.93.

(2*S*,3*S*,4*S*)-3-Buten-1-yl 2-Azido-4-[(*tert*-butyldiphenylsilyl)oxy]-4-(4-hydroxyphenyl)-3-methylbutanoate (38). To the azido ethyl ester **37** (25 mg, 0.042 mmol) in benzene (0.5 mL) was added $Ti(O\text{-}i\text{-}Pr)_4$ (0.013 mmol, 4 μL), followed by 3-buten-1-ol (0.83 mmol, 75 μL). The reaction mixture was heated to reflux for 6 h, diluted with hydrochloric acid (1 M; 1 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (1:9 ethyl acetate/hexanes) to give the butene ester **38** (20.7 mg, 91%) as a colorless oil: $[\alpha]_D$ −29.2° (*c* 0.616 in $CHCl_3$); IR (neat) 3440 (br), 3095, 2982, 2958, 2881, 2120, 1729, 1603, 1518, 1432, 1205, 1110, 1062, 925, 844, 747, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.21 (m, 10 H), 6.92, 6.60 (AB q, 4 H, *J* = 8.6 Hz), 5.79 (m, 1 H), 5.11 (br m, 2 H), 4.89 (br s, 1 H), 4.72 (d, 1 H, *J* = 2.8 Hz), 4.35 (d, 1 H, *J* = 9.5 Hz), 4.27 (m, 2 H), 2.45 (m, 3 H), 0.97 (s, 9 H), 0.41 (d, 3 H, *J* = 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 155.0, 151.0, 135.9, 135.8, 134.2, 133.7, 133.5, 133.2, 129.6, 129.4, 128.8, 127.5, 127.2, 117.7, 114.8, 91.3, 64.7, 63.0, 43.7, 33.1, 27.0, 19.5, 11.0; MS (FAB) *m/z* 542 (M − H^+), 486, 466, 389, 361, 336, 288, 260, 199; exact mass (EI) calcd for $C_{31}H_{37}N_3O_4Si$ (M − $C_4H_9^+$) 486.1850, found (M − $C_4H_9^+$) 486.1837.

(2*S*,3*S*,4*S*)-3-Buten-1-yl 2-Azido-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbutanoate (39). To the phenol **38** (136 mg, 0.25 mmol) in anhydrous THF (1 mL) at −78 °C was added 2,6-lutidine (0.50 mmol, 58 μL), followed by *t*-$BuMe_2SiOSO_2CF_3$ (0.50 mmol, 0.12 mL). The reaction mixture was allowed to warm up to 25 °C and quenched by the addition of pH 7 phosphate buffer (2 mL). The mixture was extracted with Et_2O (3 × 5 mL), and the organic layers were washed with pH 4 phthalate buffer (10 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (5:95 ethyl acetate/hexanes) to afford the

silyl ether **39** (156 mg, 95%) as a colorless oil: $[\alpha]_D$ −25° (*c* 0.44 in $CHCl_3$); IR (neat) 3098, 2980, 2956, 2920, 2880, 2128, 1751, 1618, 1519, 1480, 1470, 1438, 1400, 1362, 1265, 1197, 1115, 1077, 1011, 918, 849, 824, 783, 741, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.7–7.2 (m, 10 H), 6.95, 6.66 (AB q, 4 H, *J* = 8.4 Hz), 5.81 (m, 1 H), 5.13 (br m, 2 H), 4.73 (d, 1 H, *J* = 2.8 Hz), 4.36 (d, 1 H, *J* = 9.6 Hz), 4.28 (m, 2 H), 2.47 (m, 3 H), 0.99 (s, 9 H), 0.98 (s, 9 H), 0.41 (d, 3 H, *J* = 7.2 Hz), 0.19 (s, 3 H), 0.18 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 155.1, 150.0, 136.0, 135.9, 134.8, 133.8, 133.5, 133.2, 129.6, 129.4, 128.6, 127.5, 127.2, 119.7, 117.7, 77.2, 64.7, 63.0, 43.8, 33.1, 27.0, 25.7, 19.5, 18.2, 11.0, 1.0; MS (FAB) *m/z* 656 ($M - H^+$), 600, 503, 475, 417, 374, 336, 297, 248, 197; exact mass (EI) calcd for $C_{37}H_{51}N_3O_4Si_2$ ($M - C_4H_9^+$) 600.2716, found ($M - C_4H_9^+$) 600.2718. Anal. Calcd for $C_{37}H_{51}N_3O_4Si_2$: C, 67.54; H, 7.81; N, 6.39. Found: C, 67.70; H, 8.08; N, 6.12.

(2*S*,3*S*,4*S*)-Methyl 2-Azido-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbutanoate. To the butene ester **39** (43 mg, 0.065 mmol) in 1:1 CH_2Cl_2/MeOH (5 mL) at −78 °C was introduced ozone via a pipette until a blue color persisted. The reaction mixture was purged of excess ozone with a stream of N_2, Me_2S (1 mL) was added, and the mixture was allowed to warm up to 25 °C. After 4 h, to the crude aldehyde (^1H NMR (90 MHz, $CDCl_3$) δ 9.8) was added DBU (0.072 mmol, 11 μL), and the reaction mixture was stirred for an additional 2 h. The solution was acidified with aqueous citric acid (0.1 M), extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in Et_2O (1 mL), and to the solution at 0 °C was added an ether solution of CH_2N_2 until a yellow color persisted. The excess diazomethane was purged with a stream of N_2, and the solution was washed with H_2O (5 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (5:95 ethyl acetate/hexanes) to afford the title methyl ester (29.2 mg, 73%) as a pale yellow oil: $[\alpha]_D$ −20.7° (*c* 0.58 in $CHCl_3$); IR (neat) 3090, 2970, 2945, 2900, 2870, 2120, 1762, 1628, 1525, 1475, 1442, 1408, 1378, 1280, 1222, 1128, 1088, 1034, 932, 868, 799, 753, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.20 (m, 10 H), 6.92, 6.63 (AB q, 4 H, *J* = 8 Hz), 4.74 (d, 1 H, *J* = 2.1 Hz), 4.35 (d, 1 H, *J* = 9.2 Hz), 3.81 (s, 3 H), 2.46 (m, 3 H), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.40 (d, 3 H, *J* = 6.8 Hz), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 155.1, 136.0, 135.9, 134.7, 133.8, 133.2, 129.6, 129.4, 128.6, 127.5, 127.2, 119.7, 77.2, 63.0, 52.6, 43.8, 27.0, 25.7, 19.5, 18.2, 11.0, 5.6; MS (FAB) *m/z* 616 ($M - H^+$), 588, 560, 475, 362, 334, 296, 248, 213, 191, 183; exact mass (EI) calcd for $C_{34}H_{47}N_3O_4Si_2$ ($M - C_4H_9^+$) 560.2401, found ($M - C_4H_9^+$) 560.2399. Anal. Calcd for $C_{34}H_{47}N_3O_4Si_2$: C, 66.09; H, 7.67; N, 6.80. Found: C, 66.00; H, 7.62; N, 6.60.

(2*S*,3*S*,4*S*)-4-Nitrophenyl 2-Azido-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbutanoate (41). To a solution of the butene ester **39** (90 mg, 0.14 mmol) in 1:1 CH_2Cl_2/MeOH (4 mL) at −78 °C was introduced ozone via a pipette until a blue color persisted. The reaction mixture was purged of excess ozone with a stream of N_2, Me_2S (1 mL) was added, and the reaction mixture was allowed to warm up to 25 °C. After 4 h, DBU (0.15 mmol, 23 μL) was added and the mixture was stirred for an additional 2 h. The solution was acidifed with aqueous citric acid (0.1 M), extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and evaporated. To the crude acid in THF (1 mL) was added 4-nitrophenol (recrystallized from toluene, 0.14 mmol, 19 mg) followed by DCC (0.14 mmol, 28 mg), and the reaction mixture stirred at 25 °C for 12 h. The solution was diluted with Et_2O, filtered, and washed with brine (5 mL), and the organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (5:95 Et_2O/hexanes) to give the activated ester **41** (60 mg, 61%) as a pale yellow oil: $[\alpha]_D$ −26.2° (*c* 0.755 in $CHCl_3$); IR (neat) 3040, 2980, 2950, 2895, 2870, 2120, 1785, 1755, 1625, 1605, 1540, 1525, 1508, 1485, 1475, 1442, 1390, 1370, 1275, 1225, 1170, 1135, 1085, 920, 860, 823, 800, 760, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 2 H, *J* = 9.2 Hz), 7.7–7.2 (m, 12 H), 6.98, 6.67 (AB q, 4 H, *J* = 8 Hz), 4.98 (d, 1 H, *J* = 2.8 Hz), 4.44 (d, 1 H, *J* = 9.2 Hz), 2.62 (m, 1 H), 0.98 (s, 9 H), 0.97 (s, 9 H), 0.55 (d, 3 H, *J* = 7.2 Hz), 0.18 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 155.3, 154.8, 145.7, 136.0, 135.8, 134.3, 133.7, 133.0, 129.8, 129.6, 128.6, 127.6, 127.3, 125.3, 122.3, 119.8, 76.6, 63.1, 44.0, 27.0, 25.7, 19.5, 18.2, 1.1, 1.0; MS (FAB) *m/z* 723 ($M - H^+$) 667, 639, 611, 574, 543; exact mass (EI) calcd for $C_{39}H_{48}N_4O_6Si_2$ ($M - 4\text{-}O_2NC_6H_4^+$) 602.2870, found ($M - 4\text{-}O_2NC_6H_4^+$), 602.2880.

1-[5′-[*N*-(*tert*-Butoxycarbonyl)amino]-5′-deoxy-β-D-allofuranosyluronic acid]uracil Benzyl Ester (44). To the amino acid **17** (0.2 g, 0.7 mmol) in 1:1 dioxane/H_2O (2 mL) at 25 °C was added aqueous K_2CO_3 (1 M; 0.7 mL) followed by di-*tert*-butyl dicarbonate (0.7 mmol, 0.16 mL). After 3.5 h, the solution was acidifed with 1 M $KHSO_4$ and extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated. To the crude residue in MeOH (1 mL) at 0 °C was added phenyldiazomethane until the salmon color persisted. The solution was evaporated and chromatographed on silica gel (100% ethyl acetate to 3:9 EtOH/ethyl acetate) to yield the protected amino acid **44** (0.238 g, 72%) as a white powder: mp 162–164 °C dec; $[\alpha]_D$ +4.2° (*c* 0.96 in MeOH); IR (KBr) 3425 (br), 2995, 1695, 1517, 1466, 1394, 1375, 1268, 1167, 1100, 1070, 1027, 870, 813 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.40 (d, 1 H, *J* = 8 Hz), 7.32–7.24 (m, 5 H), 5.80 (d, 1 H, *J* = 5.2 Hz), 5.51 (d, 1 H, *J* = 8 Hz), 5.18 (d, 1 H, *J* = 12.4 Hz), 5.09 (d, 1 H, *J* = 12.4 Hz), 4.53 (d, 1 H, *J* = 5.6 Hz), 4.23 (m, 1 H), 4.13 (t, 2 H, *J* = 5.2 Hz), 1.38 (s, 9 H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.3, 165.8, 157.7, 152.2, 142.4, 136.8, 129.5, 129.4, 103.2, 90.9, 85.0, 81.2, 74.2, 71.7, 68.2, 56.6, 52.9, 28.6; MS (FAB) *m/z* 478 ($M + H^+$), 460, 444, 422, 401, 378, 355; exact mass (FAB) calcd for $C_{22}H_{27}N_3O_9$ ($M + H^+$) 478.1826, found ($M + H^+$) 478.1843. Anal. Calcd for $C_{22}H_{27}N_3O_9 \cdot 0.5H_2O$: C, 54.32; H, 5.80; N, 8.64. Found: C, 54.56; H, 5.73; N, 8.52.

1-[5′-[*N*-[(2*S*,3*S*,4*S*)-2-Azido-4-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbutanoyl]amino]-5′-deoxy-β-D-allofuranosyluronic acid]uracil Benzyl Ester (45). To the protected amino acid **44** (45 mg, 0.094 mmol) in ethyl acetate (1 mL) at 0 °C was added trifluoroacetic acid (5 mL), and the reaction mixture was allowed to warm up to 25 °C. After 30 min, the solution was evaporated and azeotroped with ethyl acetate (5 × 10 mL). To the residue in DMF (0.1 mL) was added *N*-methylmorpholine (0.19 mmol, 21 μL) followed by *p*-nitrophenyl ester **41** (0.11 mmol, 79 mg) in DMF (0.5 mL). After 3 days, the solution was acidified with 1 M $NaHSO_4$, diluted with brine (2 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (100% Et_2O to 3:97 EtOH/ethyl acetate) to give the amide **45** (47.7 mg, 53%) as a pale yellow foam: $[\alpha]_D$ −10.2° (*c* 0.98 in $CHCl_3$); IR (neat) 3365 (br), 3093, 2987, 2929, 2893, 2133, 1694, 1515, 1465, 1433, 1394, 1264, 1114, 1065, 918, 855, 811, 773, 735 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.08 (d, 1 H, *J* = 7.6 Hz), 7.49–7.26 (m, 14 H), 7.00, 6.69 (AB q, 4 H, *J* = 8.8 Hz), 5.83 (d, 1 H, *J* = 4.8 Hz), 5.54 (d, 1 H, *J* = 8 Hz), 5.15 (m, 2 H), 4.93 (m, 1 H), 4.69 (d, 1 H, *J* = 3.6 Hz), 4.47 (m, 2 H), 4.34 (m, 1 H), 4.18 (t, 1 H, *J* = 5.2 Hz), 2.84 (br s, 3 H), 2.64 (m, 1 H), 0.97 (s, 9 H), 0.94 (s, 9 H), 0.45 (d, 3 H, *J* = 6.8 Hz), 0.18 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (101 MHz, acetone-d_6) δ 170.5, 170.4, 169.8, 163.2, 156.0, 151.5, 141.7, 136.8, 136.7, 136.6, 135.7, 134.6, 134.1, 130.5, 130.4, 129.2, 129.8, 129.0, 128.4, 128.1, 120.4, 103.2, 91.2, 84.1, 78.0, 73.6, 71.5, 67.6, 64.9, 55.4, 55.0, 44.4, 31.9, 27.4, 26.0, 20.0, 18.8, 11.0; MS (FAB) *m/z* 905 ($M - C_4H_9^+$), 707, 596, 525, 475, 391, 336, 266; exact mass (FAB) calcd for $C_{50}H_{62}N_6O_{10}Si_2$ ($M - C_4H_9^+$) 905.3364, found ($M - C_4H^{9+}$) 905.3392. Anal. Calcd for $C_{50}H_{62}N_6O_{10}Si_2 \cdot H_2O$: C, 61.20; H, 6.57; N, 8.56. Found: C, 60.96; H, 6.33; N, 8.42.

Nikkomycin B (1). To the coupled product **45** (39 mg, 0.041 mmol) in anhydrous THF (0.5 mL) was added Bu_4NF (1 M in THF, 122 μL). After 30 min, the solution was concentrated and flash chromatographed on silica gel (5:95 MeOH/$CHCl_3$). To remove the tetrabutylammonium salts, the desilylated material was rechromatographed on silica gel (5:95 EtOH/ethyl acetate). The residue was dissolved in MeOH (0.5 mL) and added to an 50% aqueous methanolic suspension of 10% Pd on $BaSO_4$ (20 mg) that had been prehydrogenated overnight. The mixture was stirred at 25 °C for 30 min, filtered through Celite, and evaporated. The residue was chromatographed on cellulose powder (20 μm, 4:1:0.5–1.5 BuOH/MeOH/H_2O) to afford nikkomycin B (**1**) (7.8 mg, 39%) as a white powder: TLC (4:1:2 BuOH/AcOH/H_2O) R_f 0.35 (UV and ninhydrin active); mp 202–205 °C dec; $[\alpha]_D$ +50° (*c* 0.04 in H_2O); IR (KBr) 3800–3230 (br), 2922, 1687, 1616, 1511, 1463, 1387, 1262, 1112, 1056, 813, 669, 561 cm^{-1}; ^1H NMR (400

MHz, D_2O/CD_3OD) see table; ^{13}C NMR (101 MHz, D_2O, internal reference to CD_3OD at δ 49.0) δ 173.8, 169.5, 166.3, 155.5, 151.9, 142.2, 133.9, 128.3, 115.6, 102.6, 89.2, 84.1, 75.2, 73.1, 70.2, 56.6, 54.5, 40.9, 11.3; MS (FAB) m/z 517 (M + Na^+), 495 (M + H^+), 391, 329, 295, 237, 207, 179; exact mass (FAB) calcd for $C_{21}H_{28}N_4O_{10}$ (M + Na^+) 517.1547, (M + H^+) 495.1727, found (M + Na^+) 517.1564 (M + H^+), 495.1678.

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Supplementary Material Available: ^1H NMR spectra for compounds **28a,b**, **30a,b**, **35**, **38**, and **41** (7 pages). Ordering information is given on any current masthead page.

A Short and Facile Synthetic Route to Hydroxylated Flavones. New Syntheses of Apigenin, Tricin, and Luteolin

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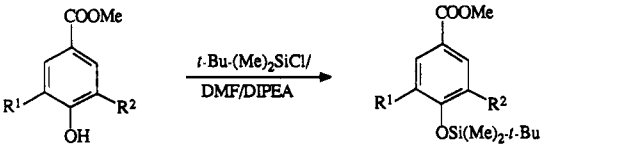
Reaction of the lithium polyanions generated from *o*-hydroxyacetophenones **3a-f** with O-silyloxylated benzoates **2a-d** gave 1-aryl-3-(2-hydroxyphenyl)-1,3-propanediones **4a-n**, which on treatment with acetic acid containing 0.5% H_2SO_4 at 95-100 °C afforded hydroxylated flavones **5-18** in high yields (76-92%).

Ring-A hydroxylated flavones are of current interest due to biological activities including inhibition of retroviral reverse transcriptases,[1-3] protein-tyrosine kinases,[4,5] and serine/threonine kinases.[4] They possess anticancer[6,7] and chemopreventative activities,[7] and certain ring-A hydroxylated flavones inhibit HIV-induced syncytium formation.[8] Although a number of methods are available for the synthesis of flavones,[9-18] they are not ideal for the preparation of ring-A hydroxylated flavones because the phenolic hydroxyl groups of the intermediates are derivatized as esters or ethers that must eventually be cleaved to regenerate the hydroxyl groups. This often results in only partial deprotection of the phenolic hydroxyl groups, which lowers the overall yield and complicates the product isolation procedure. We recently communicated a way to avoid this problem by making the lithium polyanions of di- and trihydroxylated acetophenones using enough lithium bis(trimethylsilyl)amide to deprotonate all of the phenolic hydroxyl groups and generate the lithium enolate of the ketone, followed by regioselective acylation of the carbon of the lithium enolate with an aroyl chloride to give a β-diketone intermediate directly.[19] The present report documents an investigation of the extension of this methodology in combination with *tert*-butyldimethylsilyl protection[20,21] of the ring-C phenolic hydroxyls to the preparation of a variety of flavones bearing hydroxyl groups on both the A and C rings. The desired polyhydroxylated flavones are produced in high yields, and tedious purifications are avoided. This methodology has resulted in improved syntheses of the naturally occurring flavones apigenin (**9**), luteolin (**11**), and tricin (**18**).

Scheme I



1a, $R^1 = R^2 = H$
1b, $R^1 = OH$, $R^2 = H$
1c, $R^1 = R^2 = OH$
1d, $R^1 = R^2 = OMe$

2a, $R^1 = R^2 = H$
2b, $R^1 = OSi(Me)_2$-*t*-Bu, $R^2 = H$
2c, $R^1 = R^2 = OSi(Me)_2$-*t*-Bu
2d, $R^1 = R^2 = OMe$

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