Features of the asymmetric synthesis of 3-substituted 2-*exo*-methylenecyclohexanones described here are summarized below. (1) Consistently high enantiomeric purity (ca. 90% ee) of **4** was realized as long as R_2CuLi was employed (Table I, entries 1, 3, 7, and 9), although slightly low ee (86% ee) was observed in the reaction with $(vinyl)_2CuLi$ (entry 9). Generally, the absence of $ZnBr_2$ did not affect the ee of **4** but decreased the yields of **4** or **3** to a great extent (entries 2, 4, and 10). (2) Considerable decrease of ee of **4** was noted in the reaction with R_2CuMgX (entries 5, 8, and 11). The use of *n*-BuMgCl even reversed the absolute configuration of **3b**, giving rise to (*R*)-**3b**, as did that of $(vinyl)_2CuMgBr$ (entries 6 and 11).

From these results, one plausible transition-state model can be proposed. The added Zn^{2+} or in situ generated Li^+ [17] should serve to fix the conformation of **2** by coordination to the three hetero atoms in **2**,[18] eventually shielding the *re*-face of **2** partially as illustrated in a metal-chelated conformer **5**. Due to the steric bulk of dimeric R_2CuLi complex, its addition to **5** occurred from the less hindered *si*-face,[19,20] leading to the (*S*)-(+)-**3** (R = Me, Et, *n*-Bu) and (*R*)-**3** (R = vinyl, Ph) enantiomers.[21] The use of (*R*)-**2**, as expected, resulted in the formation of the corresponding antipodal (*R*)-(−)-**3b** having the same 90% ee by reacting with *n*-Bu_2CuLi in the presence of $ZnBr_2$.

The decrease of product ee with R_2CuMgX may mainly arise from the addition of R_2CuMgX or the equilibrating counterpart RMgX to Mg^{2+}-chelated **2**, presumably taking a geometry different from **5**;[18] this reaction should yield (*R*)-**3b** (entry 6) and compete with that of R_2CuMgX complexes to **5**.

This method for optically active 3-substituted 2-*exo*-methylenecyclohexanones constitutes a new direct and simple approach to the synthesis of this important class of compounds.[22] Further, this approach provides ready access to enantiomerically enriched 2-substituted adipic acids (eq 3). Further studies using analogous 5- or 7-membered substrates as well as other nucleophiles are under investigation.

(17) LiBr was present in the reaction with R_2CuLi, since R_2CuLi was prepared from $CuBr \cdot Me_2S$ and RLi in situ.

(18) (a) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1. (b) Fujisawa, T.; Watanabe, M.; Sato, T. *Chem. Lett.* **1984**, 2055. (c) Fujisawa, T.; Funabara, M.; Ukaji, Y.; Sato, T. *Chem. Lett.* **1988**, 59.

(19) For an excellent work on a similar diastereodifferentiating asymmetric conjugate addition using metal chelation to produce 3-substituted cycloalkanones, see: (a) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180. (b) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 225. (c) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72.

(20) For enantioselective conjugate addition reactions of chiral cuprates to 2-cycloalkenones, see: (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (b) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040. (c) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 6347.

(21) As an alternative possibility, one reviewer suggested that the cuprate reagent might be directed to the alkene by coordination to the nitrogen and oxygen of the chiral auxiliary via a complex-induced proximity effect: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. We will investigate the source of the observed 1,5-stereocontrol in detail by changing Lewis acids, chiral amines, and nucleophiles and report these results in due course.

(22) (a) Herz, W.; Mitra, R. B.; Rabindran, K.; Veswanathan, N. *J. Org. Chem.* **1962**, *27*, 4041. (b) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710. (c) Murai, A.; Sato, S.; Osada, A.; Katsui, N.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1982**, 32.

Periodinane Oxidation, Selective Primary Deprotection, and Remarkably Stereoselective Reduction of *tert*-Butyldimethylsilyl-Protected Ribonucleosides. Synthesis of 9-(β-D-Xylofuranosyl)adenine or 3′-Deuterioadenosine from Adenosine[1]

Morris J. Robins,* Vicente Samano, and Mark D. Johnson

Department of Chemistry, Brigham Young University, Provo, Utah 84602

Received November 14, 1989

Summary: Treatment of 9-(2,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl)adenine (**2**) with sodium triacetoxyborohydride in acetic acid and deprotection gave adenosine (**1b**) and 9-(β-D-xylofuranosyl)adenine (**3**) [3:97 (1:32)]. Selective O5′ deprotection of **2**, and hydroxyl-directed reduction with the hydride (or deuteride) reagent gave **1b** (or 3′-deuterio, **1c**) and **3** [99.5:0.5 (199:1)] after deprotection.

Reduction of protected 2′- and 3′-ketonucleoside derivatives with sodium borohydride/alcohol affords epimeric mixtures of the corresponding nucleoside alcohols with stereoselectivity enhanced by proximity to the heterocyclic base.[2] Attack by hydride occurs predominantly at the α-face of the sugar ring trans to the base and with greater stereodifferentiation at the proximal 2′-position. Thus, reduction of 2′-ketonucleoside derivatives gives stereoselectivities of 82–95% for the arabino epimers, whereas analogous treatment of 3′-ketonucleosides gives lower selectivities for the xylo products.[2-4] We now describe remarkable stereocontrol for the synthesis of either the ribo or xylo diastereomers with sodium triacetoxyborohydride in acetic acid beginning with a common 3′-ketonucleoside intermediate.

Sodium triacetoxyborohydride is a mild reducing agent formed by addition of sodium borohydride to an excess of cold acetic acid.[5] This reagent gave chemoselective reduction of aldehydes in the presence of ketones[5a,6] and later was found to effect stereoselective reduction of cyclic[7] and acyclic[6,8] β-hydroxy ketones to the respective trans and anti

(1) This paper is Nucleic Acid Related Compounds. 58. For the previous paper in this series, see: Robins, M. J.; Wood, S. G.; Dalley, N. K.; Herdewijn, P.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 1763.

(2) Cook, A. F.; Moffatt, J. G. *J. Am. Chem. Soc.* **1967**, *89*, 2697.

(3) (a) Hansske, F.; Robins, M. J. *Tetrahedron Lett.* **1983**, *24*, 1589. (b) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125.

(4) Crews, R. P.; Baker, D. C. *Nucleosides Nucleotides* **1983**, *2*, 275.

(5) (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (b) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 3453.

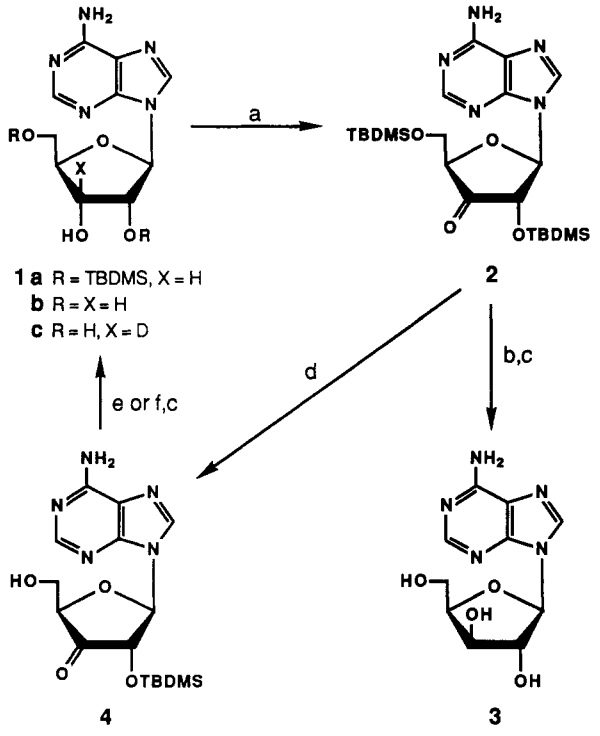
(6) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287.

(7) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (b) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.

(8) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

0022-3263/90/1955-0410$02.50/0 © 1990 American Chemical Society

Scheme I[a]



[a] (a) Dess–Martin periodinane (4 equiv)/CH_2Cl_2 (>95%); (b) $NaBH_4$ (6.5 equiv)/AcOH/~5 °C/48 h (94%); (c) Bu_4NF/THF (quant); (d) CF_3CO_2H/H_2O (9:1)/0 °C (95%); (e) $NaBH_4$ (2 equiv)/AcOH/ambient/2 h (95%); (f) $NaBD_4$ (2 equiv)/AcOH/ambient/2 h (95%).

diols. The stereochemical control was attributed to in situ formation of an alkoxydiacetoxyborohydride intermediate (by acid-catalyzed displacement of one acetoxy ligand on boron by a hydroxyl oxygen) followed by intramolecular delivery of hydride to the proximal face of the carbonyl group to produce trans or anti diols.

We have found that excess sodium triacetoxyborohydride (generated in situ at <15 °C) can reduce the isolated ketone function of 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-3′-ketoadenosine (**2**) within 48 h at ~5 °C. The xylo isomer (diastereoselectivity 32:1, xylo/ribo) was formed by hydride delivery to the α-face of the sugar ring trans to adenine. In remarkable contrast, treatment of 2′-*O*-TBDMS-3′-ketoadenosine (**4**) (obtained crystalline in 95% yield by selective removal of the 5′-*O*-TBDMS group from **2** with trifluoroacetic acid/water, 9:1, at 0 °C) with 2 equiv of the hydride reagent for 2 h at ambient temperature resulted in O5′-directed delivery of hydride from the β-face of the sugar ring to give adenosine (**1b**) (199:1 ribo/xylo diastereoselection) after deprotection. All yields in this sequence are excellent.

Ambient temperature oxidation of 2′,5′-bis-*O*-TBDMS-adenosine[9] (**1a**) with the Dess–Martin 12-I-5 periodinane reagent[10] in dichloromethane gave clean and quantitative conversion to the 3′-ketonucleoside derivative (**2**) (Scheme I). This offers an effective alternative to previously reported oxidation methods that used Pfitzner–Moffatt reagents,[2] chromium trioxide/pyridine/acetic anhydride,[3] and the Swern–Moffatt[11] system. Ready isolation of the 2-iodobenzoic acid byproducts and their reconversion to the periodinane reagent make this an economically feasible oxidant.

Treatment of the 2′,5′-bis-*O*-TBDMS-3′-ketonucleoside[3] (**2**) with 6.5 equiv of sodium triacetoxyborohydride in acetic acid (generated in situ by addition of 6.5 molar equiv of $NaBH_4$ to glacial acetic acid at <15 °C) for 48 h at ~5 °C resulted in formation of a diastereomeric mixture whose ^1H NMR spectrum had barely discernable signals for the minor ribo isomer (~3%). Deprotection [tetrabutylammonium fluoride (TBAF)/tetrahydrofuran (THF)] gave a crude mixture that was found (HPLC, reversed-phase C18 column, 15% MeOH/H_2O, direct comparison with authentic samples) to contain ~1% of adenine plus 9-(β-D-xylofuranosyl)adenine[12] (**3**)/adenosine (**1b**) (97:3). Chromatography on Dowex 1X2 (OH^-)[12] and crystallization of the pooled product fractions gave **3**/**1b** (97:3) in 94% yield. This compares favorably with a very recently reported procedure that claimed "stereospecific" reduction of an analogous 3′-ketonucleoside derivative followed by deprotection to give **3** in 43% yield for these final steps.[13]

It is known that primary silyloxy groups are cleaved under acidic conditions more readily than their secondary counterparts. Ogilvie et al.[9a] reported selective deprotection with 80% acetic acid/water, but yields of "up to 75%" were noted in comparison with monomethoxytrityl removal at 98%. Attempted partial deprotection of **2** with 80% HOAc/H_2O at ambient temperature resulted in slow deprotection and decomposition with release of adenine. Heating accelerated both processes. Treatment of **2** with trifluoroacetic acid/water (9:1) at 0 °C effected quantitative removal of the 5′-*O*-TBDMS group to give 9-(2-*O*-TBDMS-β-D-*erythro*-pentofuran-3-ulosyl)adenine[14] (**4**) as a crystalline product in 95% yield. Since this β-hydroxy ketone (**4**) underwent glycosyl cleavage upon manipulation, it was immediately subjected to reduction.

Treatment of **4** with 2 equiv of sodium triacetoxyborohydride in acetic acid (addition of 2 molar equiv of $NaBH_4$ to HOAc at <15 °C) followed by warming to ambient temperature with stirring for 2 h resulted in disappearance of starting material. Workup gave the protected diol[9a] in 95% yield. Its ^1H NMR spectrum had sharp signals for the ribonucleoside derivative only. Deprotection with TBAF/THF gave adenosine (**1b**)/**3** with a 99.5:0.5 ratio (HPLC). Repetition with sodium borodeuteride in protioacetic acid gave 3′-deuterioadenosine (95%). Less than 5% proton incorporation at C3′ was observed (^1H NMR and mass spectra; 98 atom % $NaBD_4$ used). This demonstrated tight binding of ^2H to boron in the triacetoxyborodeuteride reagent and its O5′ exchange intermediate. Complete oxidation of the 3′-hydroxyl function of **1a** by the periodinane reagent was confirmed by treatment of the resulting **2** with TBAF/THF. Decomposition of **2** to adenine occurred, and no **1b** was detected.

In summary we have demonstrated that: (1) the Dess–Martin periodinane reagent is a useful alternative to Moffatt-type and chromium(VI) oxidants for preparation of ketonucleosides; (2) selective O5′ solvolysis of TBDMS-protected nucleosides can be effected cleanly with 90% trifluoroacetic acid at 0 °C; (3) sodium triacetoxyborohydride/acetic acid at ~5 °C effects reduction of the isolated carbonyl group of a protected 3′-ketonucleoside

(9) (a) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768. (b) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Can. J. Chem.* **1982**, *60*, 1106.

(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(11) Matsuda, A.; Itoh, H.; Takenuki, K.; Sasaki, T.; Ueda, T. *Chem. Pharm. Bull.* **1988**, *36*, 945.

(12) Robins, M. J.; Fouron, Y.; Mengel, R. *J. Org. Chem.* **1974**, *39*, 1564.

(13) Cheng, X.; Zhang, J.-D.; Zhang, L.-H. *Synthesis* **1989**, 383.

(14) **4**: ^1H NMR (Me_2SO-d_6, Me_4Si) δ −0.10 (s, 6, $SiMe_2$), 0.70 (s, 9, Si-*t*-Bu), 3.70 (br m, 2, H5′,5″), 4.43 (br s, 1, H4′), 5.07 (d, $J_{2'-1'}$ = 8.3 Hz, 1, H2′), 5.59 (dd, $J_{OH-5'}$ = 6.9 Hz, $J_{OH-5''}$ = 4.8 Hz, 1, OH5′), 6.18 (d, $J_{1'-2'}$ = 8.3 Hz, 1, H1′), 7.47 (br s, 2, NH_2), 7.47 (s, 1, H2), 8.17 (s, 1, H8).

with highly diastereoselective (1:32) α-face delivery trans to the heterocyclic base; (4) the 5'-hydroxyl group of a nucleoside acts as a β-face directing replacement ligand at boron to effect reversed diastereoselectivity (199:1) by intramolecular hydride delivery; and (5) substitution of sodium borodeuteride gives a reagent with tightly bound isotope that provides 3'-labeled ribonucleosides with virtually complete stereoselectivity. Synthetic details of these ambient or lower temperature procedures, spectroscopic data, and applications of stereodirected reductions with other sites, functional groups, and nucleosides will be reported.

Acknowledgment. We thank the American Cancer Society (CH-405) and Brigham Young University development funds for generous support.

Complex Pyrrolidines via a Tandem Michael Reaction/1,3-Dipolar Cycloaddition Sequence. A Novel Method for the Generation of Unsymmetrical Azomethine Ylides

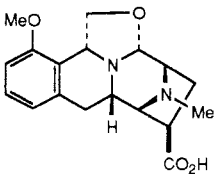
Philip Garner,* Fariba Arya, and Wen-Bin Ho

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-2699

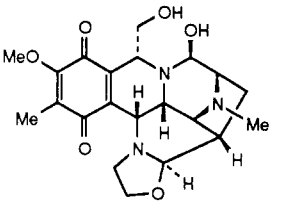
Received November 27, 1989

Summary: A novel tandem Michael addition/1,3-dipolar cycloaddition protocol for the assembly of the 3,8-diazabicyclo[3.2.1]octane ring system found in naphthyridinomycin (1) and quinocarcin (2) is described.

We recently presented a synthetic approach to the 3,8-diazabicyclo[3.2.1]octane ring systems of quinocarcin (1) and naphthyridinomycin (2) based on the 1,3-dipolar

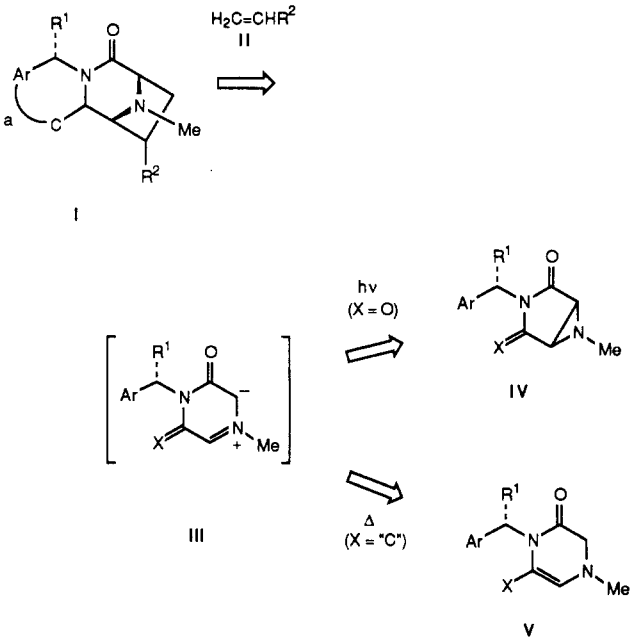


1



2

cycloaddition of symmetrical (but chiral) azomethine ylides III (X = O) available via photochemical opening of aziridines such as IV.[1,2] We envisioned a variation on this strategy that would involve the generation and regioselective trapping of unsymmetrical azomethine ylides III (X = "C") to produce cycloadducts I already differentiated for isoquinoline formation (cf. connection "a").[3] It was anticipated that this net transformation might be accomplished thermally starting from tetrahydropyrazinones V even though this entry to azomethine ylides from enamine-like structures had not been generally exploited.[4] We now report a realization of this goal which takes the form of a novel tandem Michael reaction/1,3-dipolar cycloaddition sequence.[4a,5] Even though this preliminary disclosure will focus on an achiral model substrate (i.e. R^1 = H), the strategy does allow for incorporation of a hydroxymethyl substituent (or some surrogate thereof) at this position as required by the target structures 1 and 2.



I

III

IV

V

Tetrahydropyrazinone 11 was prepared in seven steps from sarcosine (3) as shown in Scheme I. The first three transformations were uneventful and led to the production of the oily amine 6 in 54% overall yield.[6] Alkylation of this substance with bromoacetaldehyde diethyl acetal in hot benzene + triethylamine produced the amino acetal 7 in 87% yield. Treatment of 7 with 6 N HCl resulted in hydrolysis of the acetal and cyclization to the α-amido alcohol 8, mp 104–105 °C, which was isolated in 63% yield. Such harsh conditions were necessitated by the presence of a basic amine group α to the acetal.[7] Amidoalkylation of 8 was achieved by the combined action of (trimethylsilyl)cyanide and boron trifluoride etherate,[8] with the α-amido nitrile 9, mp 85–87 °C, being isolated in 72% yield after flash chromatography along with a minor amount of the isomeric α-amino nitrile 10.[9] These two regioisomers

(1) (a) Garner, P.; Sunitha, K.; Shanthilal, P. *Tetrahedron Lett.* **1988**, 3525. (b) Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041. Back references for both targets (and related substances) are cited in these papers.

(2) For a recent and comprehensive review of the known methods for generating azomethine ylides, see: Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.

(3) Joule and his co-workers successfully addressed this same issue via the regioselective cycloaddition of a related 2-oxidopyrazinium species: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, 2187.

(4) Cf. (a) Menachery, M. D.; Carroll, P.; Cava, M. P. *Tetrahedron Lett.* **1983**, 167. (b) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, 4067. (c) Kanemasa, S.; Tokenaka, S.; Watanabe, H.; Tsuge, O. *J. Org. Chem.* **1989**, *54*, 420.

(5) A conceptually similar tandem conjugate addition/1,3-dipolar cycloaddition process involving nitrones has been observed by Grigg and his co-workers. Cf.: Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325 and references cited therein.

(6) Satisfactory IR, ^{1}H and ^{13}C NMR, and HRMS analyses have been obtained for all substances shown.

(7) Cf. Massa, S.; Mai, A.; Corelli, F. *Tetrahedron Lett.* **1988**, 6471.

(8) Asher, V.; Becu, C.; Anteunis, M. J. O.; Callens, R. *Tetrahedron Lett.* **1981**, 141.

0022-3263/90/1955-0412$02.50/0 © 1990 American Chemical Society