Organocerium Additions to 2'-Deoxy-3'-ketonucleosides

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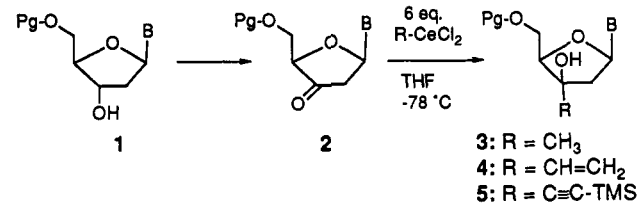
Received January 2, 1992

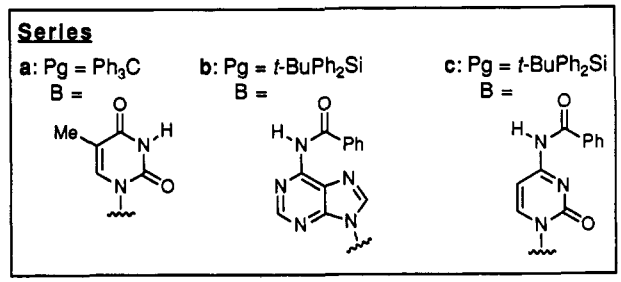
Summary: Organocerium reagents undergo efficient and highly diastereoselective carbonyl addition reactions with 2'-deoxy-3'-ketonucleosides derived from thymidine, 2'-deoxycytidine, and 2'-deoxyadenosine.

In connection with a project directed toward the synthesis of new oligodeoxynucleotide analogues, we desired an efficient and direct method for C–C bond formation at C-3' of 2'-deoxynucleosides. Among the various options that are available,[1,2] organometallic additions to 3'-ketonucleosides **2** appeared to be an attractive possibility. At the outset of this work, however, only the ketothymidine **2a** was known in the literature,[3] and the well-documented[3,4] sensitivity of **2a** toward the β-elimination of thymine had, with two exceptions,[5] thwarted previous efforts to add organometallic reagents to the carbonyl function. Herein we report that organocerium reagents, which have become established as nonbasic highly-nucleophilic reagents for carbonyl additions,[6] undergo facile additions to ketothymidine **2a**. In the course of our investigation, Robins and Samano reported that the Dess–Martin periodane[7] was a superior oxidant for the preparation of ketonucleosides,[8] and this observation has allowed us to extend the scope of our method. Specifically, the previously unreported 3'-keto-2'-deoxy adenosine **2b** and 3'-keto-2'-deoxy cytidine **2c**, despite their extreme propensity toward β-elimination, are readily prepared in greater than 90% yield by periodinane oxidation of the corresponding protected 2'-deoxynucleosides **1** (Scheme I).[9,10]

We examined organocerium reagents derived from MeMgBr, CH_2=CHMgBr, and Me_3SiC≡CLi and $CeCl_3$ (1:1) as representatives of sp^3, sp^2, and sp carbon nucleophiles. In the case of the relatively stable ketothymidine **2a**, excellent yields of the addition products were obtained in all three cases (**3a**, 93%, **4a**, 91%; **5a**, 91%), whereas the more sensitive ketoadenosine **2b** afforded somewhat lower yields of the addition products (**3b**, 63%; **4b**, 60%; **5b**, 48%).[11] Although we have only limited data on the ketocytidine **2c**, it appears to be intermediate in stability and provided the methyl addition product **3c** in 76% yield. In each case, the addition product consists of a single

Scheme I





diastereomer, within the limits of detectability. Difference NOE experiments on adduct **3b** clearly established the configuration at C-3' to be as shown, in agreement with expectation.[4]

Our general procedure for the addition of organocerium reagents to the ketonucleosides **2** is as follows: $CeCl_3 \cdot 7H_2O$ (6 equiv) was dried at 140 °C under vacuum (<1 mmHg) for at least 4 h. After the resulting powder was cooled under an argon atmosphere, cool[12] THF was added and the mixture was stirred for about 16 h. The resulting mixture was cooled to −78 °C whereupon the organometallic reagent (6 equiv) was added. The mixture was stirred for 1 h, and then a precooled (−78 °C) solution of the ketonucleoside in THF was added via Teflon cannula.

(1) For recent additions of CN^- to various C3'-electrophilic species, see: (a) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 855–862. (b) Fleet, G. W. F.; Son, J. C.; Derome, A. E. *Tetrahedron* **1988**, *44*, 625–636. (c) Greengrass, C. W.; Hoople, D. W. T.; Street, S. D. A.; Hamilton, F.; Marriot, M. S.; Bordner, J.; Dalgleish, A. G.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1989**, *32*, 618–622.

(2) For free-radical-based approaches, see: (a) Fiandor, J.; Tam, S. Y. *Tetrahedron Lett.* **1990**, *31*, 597–600. (b) Yu, D.; d'Alarcao, M. *J. Org. Chem.* **1989**, *54*, 3240–3242. (c) Chu, C. K.; Doboszewski, B.; Schmidt, W.; Ullas, G. V. *J. Org. Chem.* **1989**, *54*, 2767–2769.

(3) Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125–135.

(4) (a) Webb, T. R. *Tetrahedron Lett.* **1988**, *29*, 3769–3772. (b) Sharma, M.; Bobek, M. *Tetrahedron Lett.* **1990**, *31*, 5839–5842.

(5) (a) Webb[4a] found that, although MeMgCl, MeLi, and Me_3Al resulted in β-elimination, a Me_3Al–MeMgCl combination afforded the desired addition product. (b) Sharma and Bobek[4b] found that methylenation with $Zn/CH_2Br_2/TiCl_4$ was successful, whereas attempted addition of a Wittig reagent resulted in β-elimination.

(6) Reviews: (a) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747–752. (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573–6614.

(7) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287 and references cited therein.

(8) Robins, M. J.; Samano, V. *J. Org. Chem.* **1990**, *55*, 5186–5188.

(9) The method of Robins and Samano[8] was employed for the preparation of **2b** and **2c** with only minor modifications, as described in the following procedure for **2b**. To a solution of 119.1 mg (0.20 mmol) of **1b** in 3 mL CH_2Cl_2 at 0 °C was added Dess–Martin periodinane reagent (255 mg, 0.60 mmol) as a powder, and the mixture was stirred at 0 °C. After 30 min, the ice bath was removed and the reaction was stirred for 90 min (until starting material was consumed according to TLC analysis). The reaction was partitioned between ethyl acetate and 10 mL of saturated aqueous $NaHCO_3$ containing 1.5 g of sodium thiosulfate and was shaken vigorously for 2–3 min. The organic layer was washed consecutively with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The combined aqueous layers were extracted once with ethyl acetate. The organic layers were combined, dried (anhydrous Na_2SO_4), and concentrated in vacuo (≤25 °C) to give 110.1 mg (92%) of **2b** as an amorphous solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1 H, C_8-H), 8.34 (s, 1 H, C_2-H), 8.04 (d, 7.1 Hz, 2 H, Ar H), 7.7-7.2 (m, 13 H, Ar H), 6.68 (t, J = 7.2 Hz, 1 H, C_1-H), 4.3 (t, J = 2.8 Hz, 1 H, C_4-H), 4.04 (d, J = 2.8 Hz, 2 H, C_5-H's), 3.25 (d, J = 7.2 Hz, 2 H, C_2-H's), 1.01 (s, 9 H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 164.4, 152.8, 152.3, 151.6, 149.7, 140.8, 135.6, 135.4, 133.7, 132.8, 132.3, 129.9, 129.2, 128.9, 127.8, 127.8, 123.4, 107.9, 85.4, 83.2, 81.2, 63.4, 42.7, 26.9, 19.3. A typical ratio of product to β-elimination in the unpurified product is 20:1 as determined by ^1H NMR. Attempts to purify this sensitive material resulted in a loss of material without gain in purity.

(10) The periodinane is extremely sensitive to moisture with concomitant loss of activity. In several instances, the cause of failed oxidation reactions was determined to be hydrolytic deactivation of the periodinane reagent.

(11) Although we have found that, in several instances, employing significantly less than 6 equiv of the organocerium reagent led to incomplete conversion under our standard reaction conditions, we have not attempted to modify the reaction conditions to minimize the excess of organocerium reagent.

(12) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

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After 30 min at −78 °C, the reaction was quenched by addition of glacial acetic acid (ca. 15 equiv). The reaction was partitioned between ethyl acetate and 2 M phosphate buffer (pH 7). The aqueous layer was extracted thrice with ethyl acetate, and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography provided the alcohols **3–5** as amorphous solids, which were homogeneous by ^1H NMR, ^{13}C NMR, and HPLC analysis.

In summary, organocerium additions to 2′-deoxy 3′-ketonucleosides provide general access to an interesting class of nucleoside derivatives not previously accessible in a direct way. Studies underway in our laboratory are focused on extending the scope of the two-step sequence and on the conversion of the adducts to biologically interesting nucleoside and oligonucleotide analogues.

Acknowledgment. We are grateful to the National Institutes of Health (AI29335) for generous financial support.

Supplementary Material Available: Experimental details and spectroscopic characteristics for all new compounds (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Total Synthesis of (−)-Urdamycinone B through Polyketide Condensation

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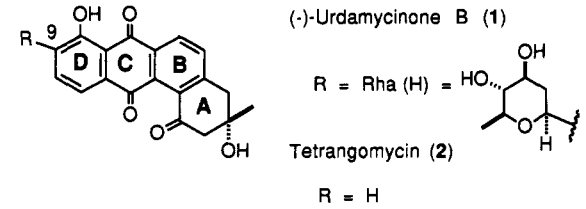
Received December 30, 1991

Summary: (−)-Urdamycinone B, the enantiomer of a natural antitumor antibiotic, was synthesized by employing polyketide condensation reactions.

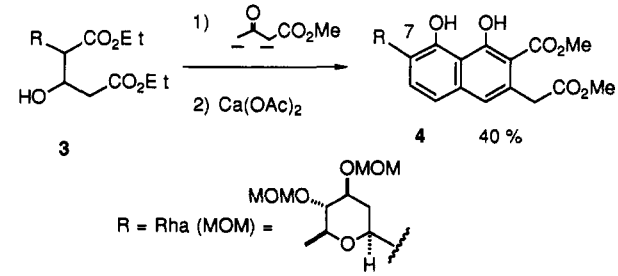
C-Glycoside angucycline is a relatively large group of antitumor antibiotics. Structurally, they are of polyketide origin possessing benz[*a*]anthracene nuclei with one C-glycosidic linkage at the 9-position and several O-glycosidic linkages.[1] Urdamycin B was isolated from *Streptomyces fradie*[2] and was converted to urdamycinone B (**1**) by a careful cleavage of *O*-glycoside bonds; the aglycon also showed antitumor activities (Chart I). We now wish to report the first total synthesis of a member of this antibiotic group. Synthesis of (−)-**1**, the enantiomer of the natural urdamycinone B, fully utilizes polyketide condensation reactions.[3]

Claisen condensation of a β-hydroxyglutarate **3** with acetoacetate dianion followed by $Ca(OAc)_2$-promoted aromatization gave a 1,8-naphthalenediol **4** with a β-*C*-glycoside linkage at the 7-position in 40% yield (Scheme I).[4] The construction of the C- and D-ring of (−)-**1** was thus achieved in short steps. Synthesis of the A and B rings was conducted based on the following strategy: (i) conversion of the aliphatic carboxylate of **4** to a methyl ketone and introduction of an acetylacetone unit to the aromatic carboxylate and (ii) controlled intramolecular aldol reaction of the resulted polyketide derivative.

Chart I



Scheme I



The strategy was examined first by the synthesis of (±)-tetrangomycin (**2**)[5] from keto ester **5**,[6] which lacks the *C*-glycoside moiety (Scheme II). De-*tert*-butoxycarbonylation, lactonization with K_2CO_3, and protection of the phenolic hydroxy group with MOM ether gave an enol lactone **6**. The aromatic carboxylate was reduced to aldehyde with DIBAL to prepare for the subsequent introduction of the acetylacetone unit. Lithiated acetylacetone monothioketal added to the aldehyde carbonyl of keto aldehyde **7** chemoselectively, and aromatization in the presence of K_2CO_3 gave anthracene **8** in 52% yield. Although the acetylacetone dianion also reacted effectively with **7**, the trials of the aromatization encountered side reactions such as retro-Claisen condensation. Anthraquinone **9** was synthesized from **8** by the deprotection of the MOM group, quinone formation by aerobic oxidation[3]

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(1) Examples of C-glycosidic angucycline antibiotics. Aquayamycin: Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171. Vineomycin A_1 (P-1894B): Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *J. Antibiot.* **1982**, *35*, 602. Ohta, K.; Okazaki, H.; Kishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 762. Kerriamycins: Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 960. Saquayamycins: Uchida, T.; Imoto, M. Watanabe, Y.; Miura, K.; Dobashi, T.; Matsuda, N.; Sawa, T.; Nakagawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1171. Capoamycin: Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 957. OM-4842: Omura, S.; Nakagawa, A.; Fukamachi, N.; Miura, S.; Takahashi, Y.; Komiyama, K.; Kobayashi, B. *J. Antibiot.* **1988**, *41*, 812.

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(5) Kuntsmann, M. P.; Mitscher, L. A. *J. Org. Chem.* **1966**, *31*, 2920.

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