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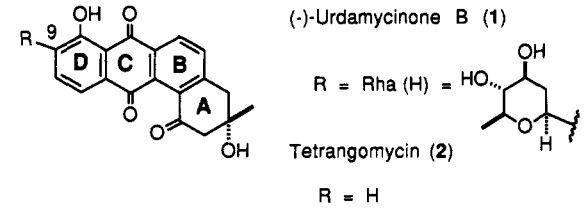
Summary: (−)-Urdamycinone B, the enantiomer of a natural antitumor antibiotic, was synthesized by employing polyketide condensation reactions.

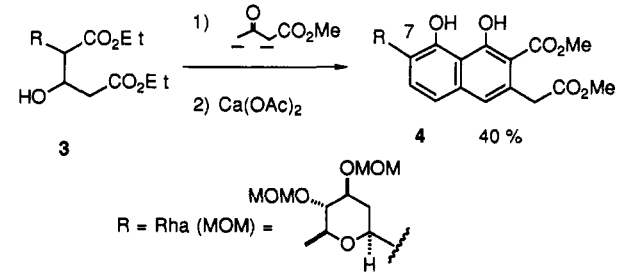
C-Glycoside angucycline is a relatively large group of antitumor antibiotics. Structurally, they are of polyketide origin possessing benz[*a*]anthracene nuclei with one C-glycosidic linkage at the 9-position and several O-glycosidic linkages.[1] Urdamycin B was isolated from *Streptomyces fradie*[2] 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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(3) Yamaguchi, M.; Hasebe, K.; Higashi, H.; Uchida, M.; Irie, A.; Minami, T. *J. Org. Chem.* **1990**, *55*, 1611 and references cited therein.

(4) Details of the regio- and stereoselective synthesis of aryl *C*-glycoside will be described elsewhere: Yamaguchi, M.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Chem. Soc., Chem. Commun.*, in press.

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

(6) Yamaguchi, M.; Nakamura, S.; Okuma, T.; Minami, T. *Tetrahedron Lett.* **1990**, *31*, 3913.

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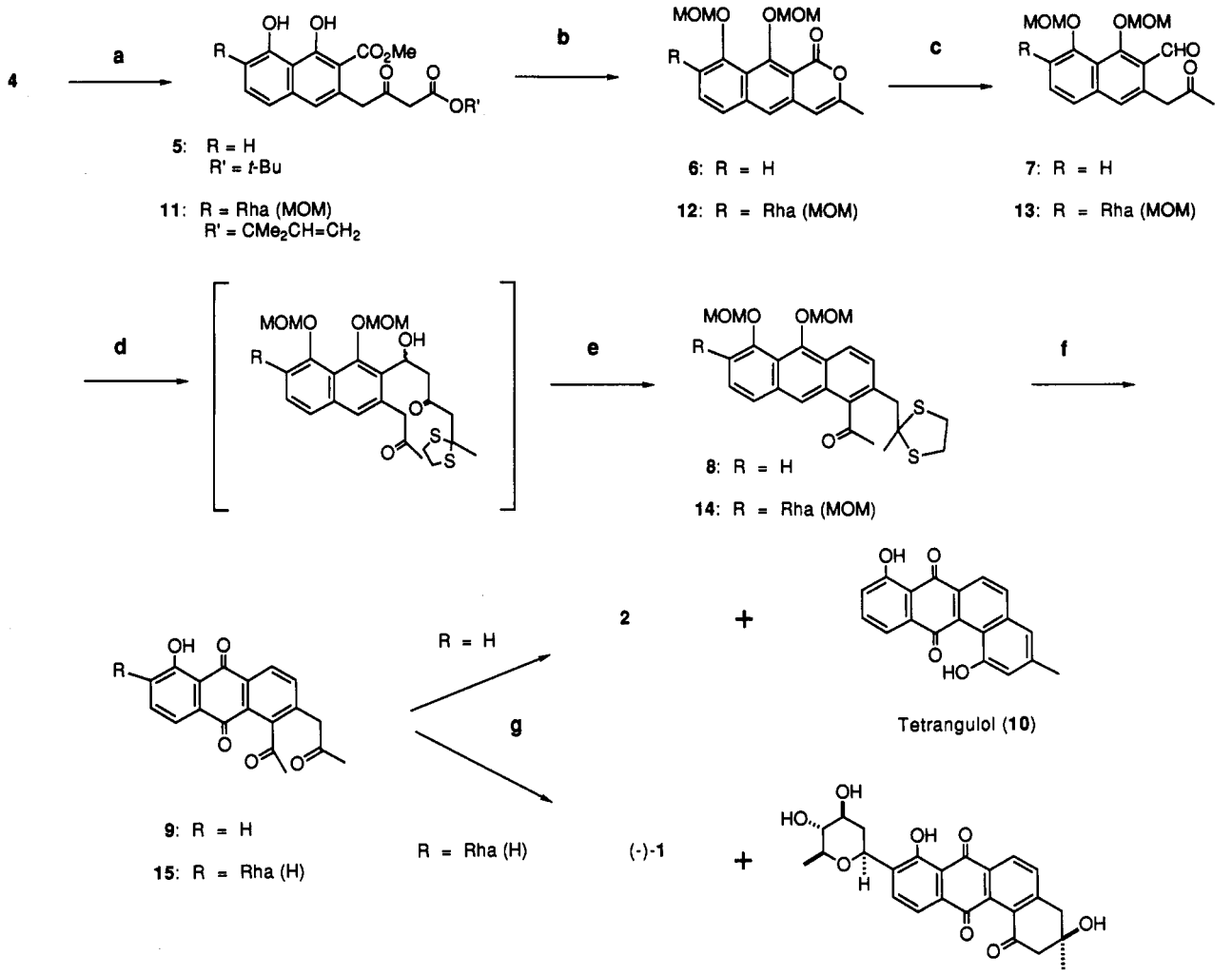
Scheme II[a]



[a] Key: (a) LDA, $CH_3CO_2CMe_2CH{=}CH_2$, THF, −78 °C to rt 12 h (R = Rha(MOM)); 88%; (b) in the case of R = H: (i) TFA, CH_2Cl_2, rt, 14 h; (ii) C_6H_6, refl., 5 h; 94% (2 steps); (iii) K_2CO_3, MeOH, rt, 2 h; (iv) MOMCl, Et_3N, CH_2Cl_2, rt, 5 h; 90% (2 steps); in the case of R = Rha(MOM): (i) $Pd(OAc)_2$, PPh_3, $HCO_2^-Et_3NH^+$, THF, rt, 30 min; (ii) K_2CO_3, MeOH, rt, 2 h; (iii) MOMCl, Et_3N, CH_2Cl_2, rt, 2 h; 83% (3 steps); (c) DIBAL, THF, −78 °C, 1 h; 91% (R = H), 80% (R = Rha(MOM)); (d) LDA, $CH_3COCH_2C(SCH_2CH_2S)CH_3$, THF, −78 °C to rt, 9 h; (e) K_2CO_3, MeOH, rt, 2 h; 52% (R = H), 60% (R = Rha(MOM)); (f) (i) HCl, MeOH, rt, 5 h; (ii) O_2, Triton B, MeOH, rt, 12 h (R = H), 36 h (R = Rha(H)); 74% (R = H, 2 steps), 83% (R = Rha(H), 2 steps); (iii) NBS, CH_3CN, H_2O, rt, 4 h; 81% (R = H), 63% (R = Rha(H)); (g) NaOH, MeOH, −25 °C, 2.5 h; 77% (R = H), 34% of (−)-1 and 37% of the diastereomer (R = Rha(H)).

in the presence of Triton B, and the oxidative removal of thioketal. As was expected, the intramolecular aldol reaction of **9** suffered from irreversible dehydration–aromatization to tetrangulol (**10**).[7] After a number of experiments, treatment with NaOH in methanol at −25 °C was found to give **2** in 77% yield.[8] The synthesis was confirmed by comparison of the NMR, IR, and UV spectra with the literature data.[5]

Synthesis of C-glycosidic anthraquinone **15** from the *C*-glycoside **4** followed the above route with a slight modification (Scheme II): Glutarate **4** was converted to keto ester **11** with lithiated 2-methyl-3-buten-2-yl acetate and dealkoxycarbonylated with a palladium catalyst.[6] Use of *tert*-butyl acetate resulted in decomposition at the thermal decarboxylation step. Keto aldehyde **13** was synthesized via an enol lactone **12**. Treatment of **13** with lithiated acetylacetone monothioketal followed by K_2CO_3-promoted aromatization gave C-glycosidic anthracene **14** in 60% yield. *C*-Glycoside anthraquinone **15** was obtained by the removal of the protecting group, oxidation, and dethioketalization. The final intramolecular aldol reaction was conducted with NaOH–MeOH at low temperature. Fortunately, the resulting stereoisomers containing the remote asymmetric centers were separable by reversed-phase chromatography giving (−)-**1** (34%) and the diastereomer (37%). Although both compounds showed very similar 270-MHz H-NMR, IR, MS, and UV spectra, which coincided with the natural product,[2] CD spectra differed significantly. That of the faster moving isomer agreed with natural urdamycinone B except that the sign was the opposite.

To summarize, the utility of polyketide condensation reactions for the construction of polyoxygenated polycyclic aromatic nuclei and *C*-glycoside linkage has been demonstrated. It should also be noted that the synthesis has disclosed chemical properties of polyketide compounds,

(7) Synthesis of **10** was reported: Brown, P. M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 997.

(8) The treatment of **9** with K_2CO_3 at 0 °C in methanol exclusively gave **10**. Equal amounts of **2** and **10** were obtained with NaOMe at −25 °C. Use of NaOH in the formation of β-hydroxy ketones by the intramolecular aldol reaction has been reported. For examples: Harris, T. M.; Webb, A. D.; Harris, C. M.; Wittek, P. J.; Murray, T. P. *J. Am. Chem. Soc.* **1976**, *98*, 6065. Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.

hypothetical biosynthetic intermediates of aromatic natural products.

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Articles

Synthesis of 3-Vinyl-1,2,4-trioxolanes by a [3 + 2] Cycloaddition of Carbonyl Oxides with α,β-Unsaturated Carbonyl Compounds

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The [3 + 2] cycloaddition of a carbonyl oxide, generated by the ozonolysis of a vinyl ether, to an α,β-unsaturated aldehyde gave the 3-vinyl-1,2,4-trioxolane (α-vinyl ozonide) in moderate yield. In contrast, α,β-unsaturated ketones showed a very poor reactivity with carbonyl oxides. Benzylidenecyclohexanones were exceptions, from which the corresponding 3-vinyl-1,2,4-trioxolanes were obtained in excellent yields. Reaction of the 3-vinyl-1,2,4-trioxolanes with ozone led to the formation of the corresponding diozonides.

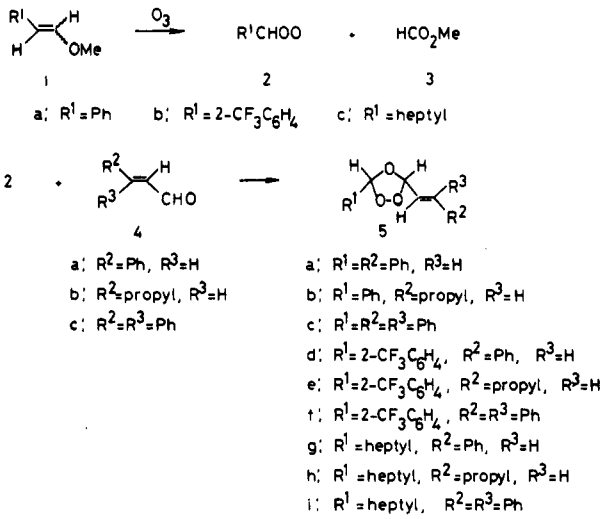
Ozonides (1,2,4-trioxolanes) continue to present a synthetic challenge.[1] Griesbaum et al. found that 3-vinyl-1,2,4-trioxolanes, prepared by the monoozonolysis of the corresponding 1,3-butadienes, constitute an interesting class of cyclic peroxides that can serve as precursors to a variety of functionalized 1,2,4-trioxolanes.[2] In developing an alternative method for the synthesis of 3-vinyl-1,2,4-trioxolanes, we conducted ozonolyses of vinyl ethers in the presence of α,β-unsaturated carbonyl compounds. Kuczkowski[3] and we[4] have found that ozonolysis of a vinyl ether in the presence of an added 1,3-dipolarophile reveals a consistent reactivity of the carbonyl oxide toward the added substrate. The reaction of vinyl ethers and ozone proceeds with virtually complete regioselectivity to give the carbonyl oxide–ester pairs,[5] and the esters show relatively low reactivity toward the carbonyl oxides.

Results and Discussion

Ozonolysis of a Vinyl Ether in the Presence of an α,β-Unsaturated Aldehyde. Ozonolysis of 1-phenyl-2-methoxyethene (**1a**) in the presence of *trans*-cinnamaldehyde (**4a**) in methylene chloride or in ether gave 3-phenyl-5-(2-phenylvinyl)-1,2,4-trioxolane (**5a**) in ca. 40% yield (Scheme I and Table I). It is interesting to note, however, that ozonolysis of 1,4-diphenyl-1,3-butadiene in methylene chloride yields a mixture of 3,6-distyryl-1,2,4,5-tetroxane (the dimer of cinnamaldehyde *O*-oxide) and benzaldehyde instead of the expected ozonide **5a**.[6]

From the reactions of **1a–c** with ozone in the presence of α,β-unsaturated aldehydes **4a–c**, the corresponding ozonides (1,2,4-trioxolanes) **5b–i** were obtained in 12–71% yield as mixture of *cis*- and *trans*-isomers (Table I). Tentative assignment of the stereochemistry of the isomeric ozonides was based on the observation that in the

Scheme I



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